RE.N.A.U.

RESURCOR

Actualités 2019 dans les SCA

CHU GRENOBLE ALPES

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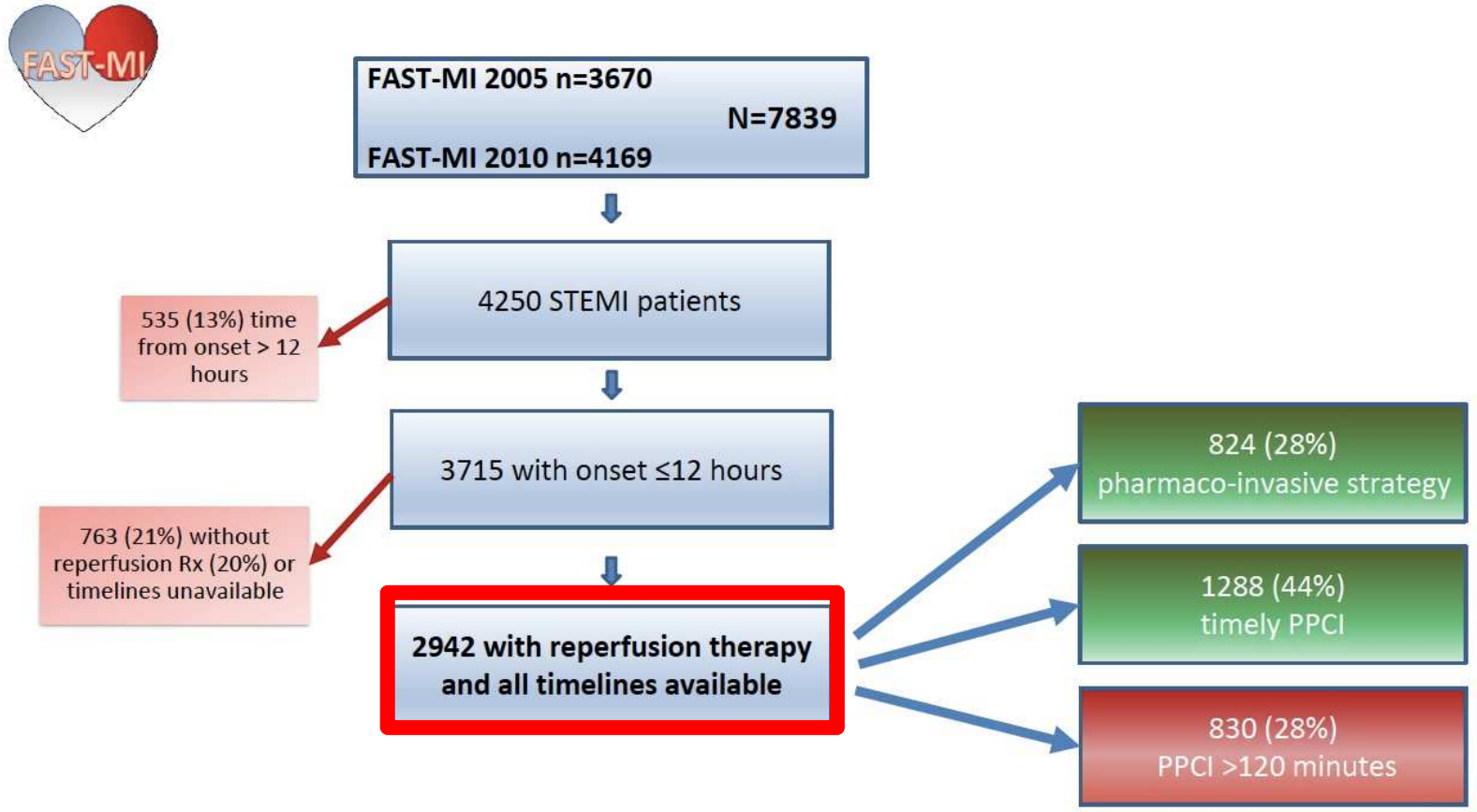
Sommaire

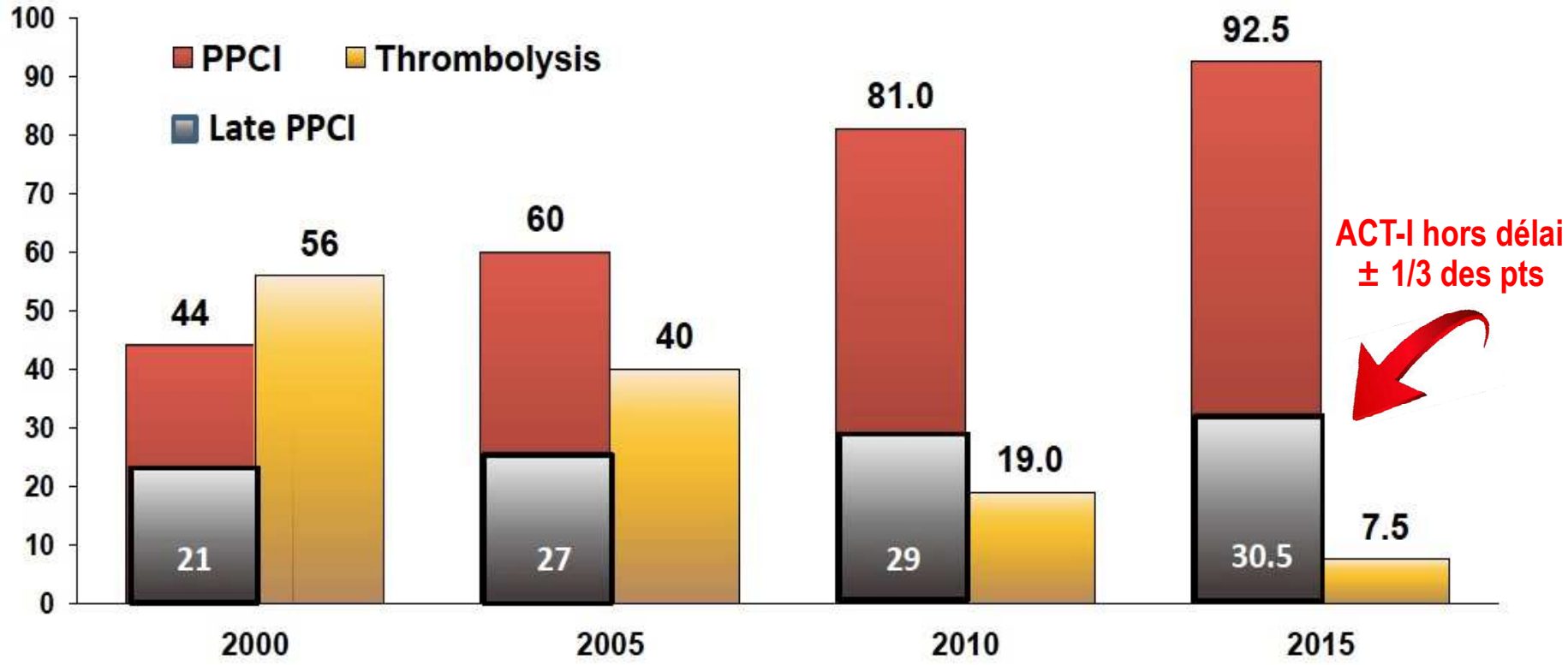
- **STEMI**
  - FAST-MI : *Il y a t-il encore une place pour la thrombolyse en 2020 ?*
  - CONDI2-ERIC-PPCI: *La fin du concept de préconditionnement ?*
  - COMPARE & COMPLETE : *Comment et quand revasculariser un tritronculaire ?*
  - COLCOT : *Sur la piste de l'inflammation après STEMI ?*

- **P2Y12 et SCA : Prasugrel, Ticagrelor… ou Clopidogrel ???**
  - ISAR-REACT 5 : *Triton ou Plato ?*
  - POPULAR-AGE : *Et si on repassait au Clopidogrel chez les SCA non-ST+ > 70 ans ?*
  - TWIGHLIGHT : *Et pourquoi pas Ticagrelor seul après 3 mois ???*

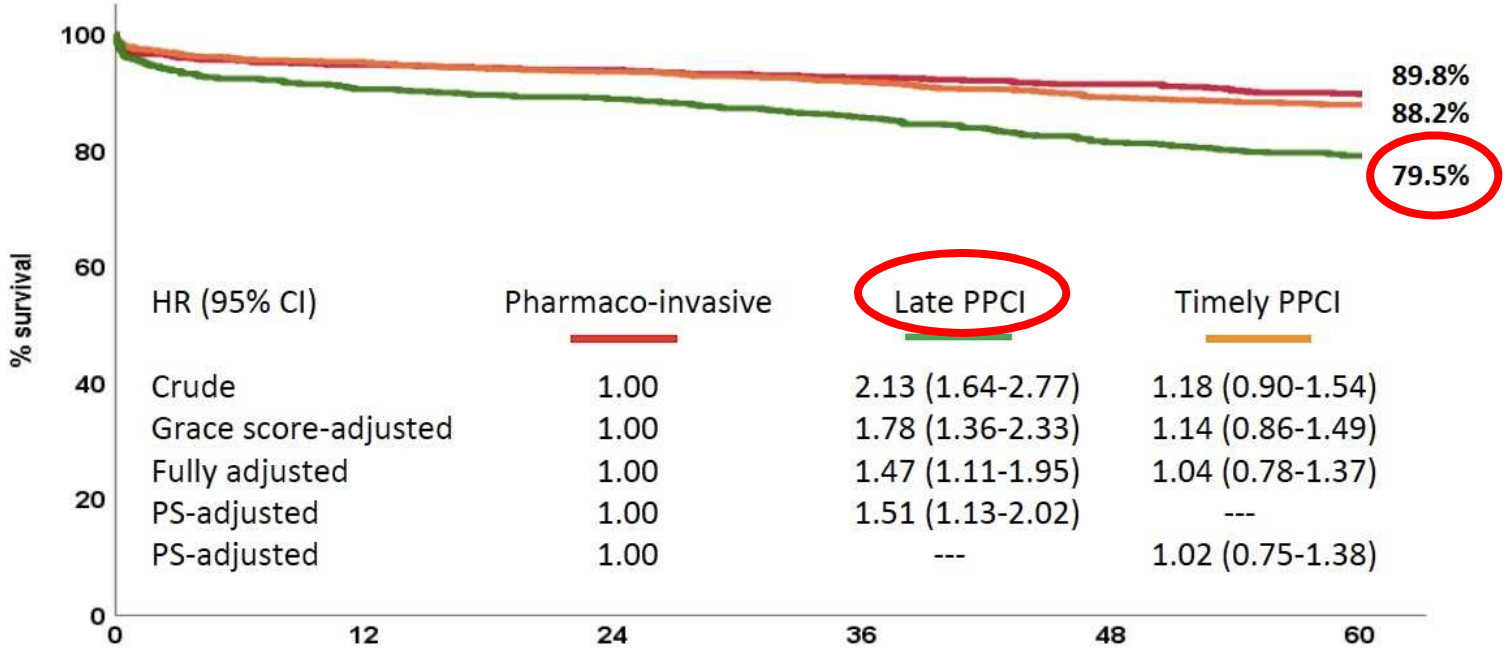
FAST-MI


FAST-MI
FAST-MI 2005 n=3670
N=7839
FAST-MI 2010 n=4169
4250 STEMI patients
535 (13%) time from onset > 12 hours
3715 with onset ≤12 hours
763 (21%) without reperfusion Rx (20%) or timelines unavailable
2942 with reperfusion therapy and all timelines available
824 (28%) pharmaco-invasive strategy
1288 (44%) timely PPCI
830 (28%) PPCI >120 minutes

FAST-MI : Evolution des méthodes de reperfusion

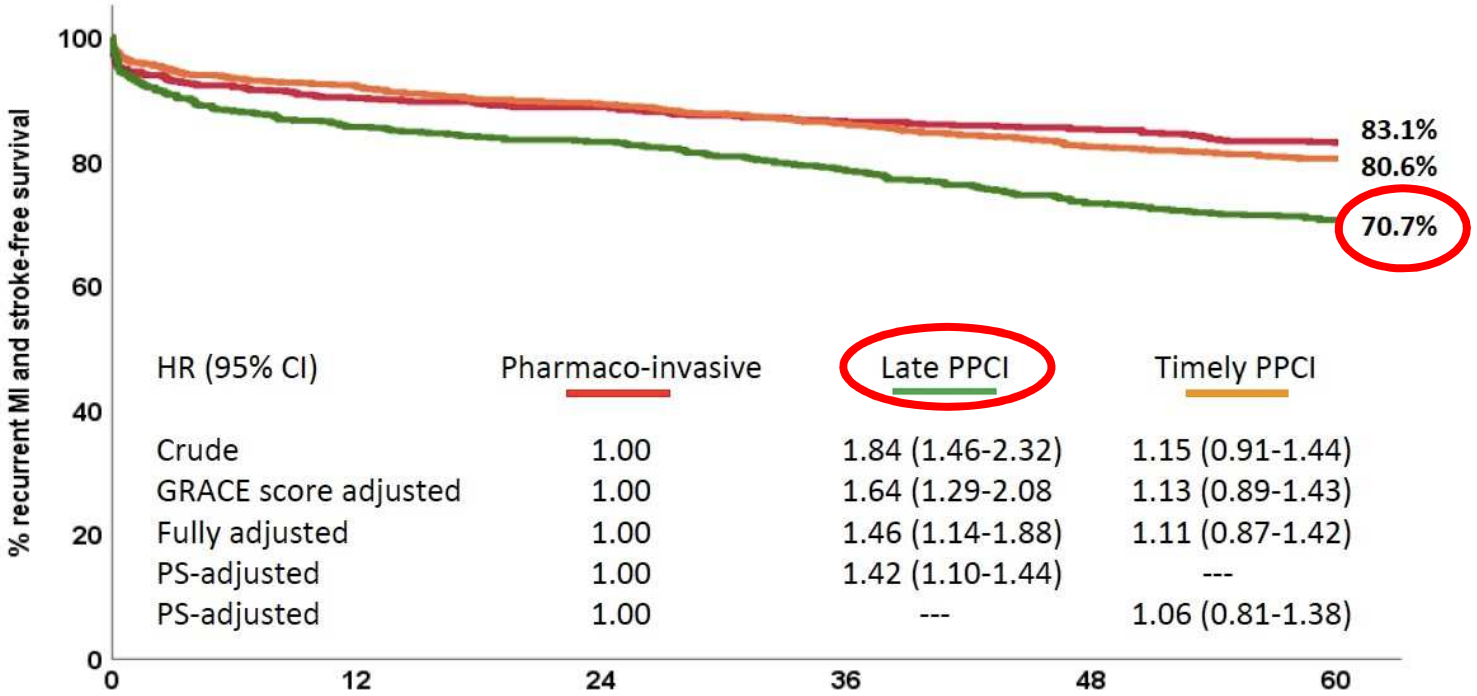


FAST-MI : Survie à 5 ans selon le type de reperfusion



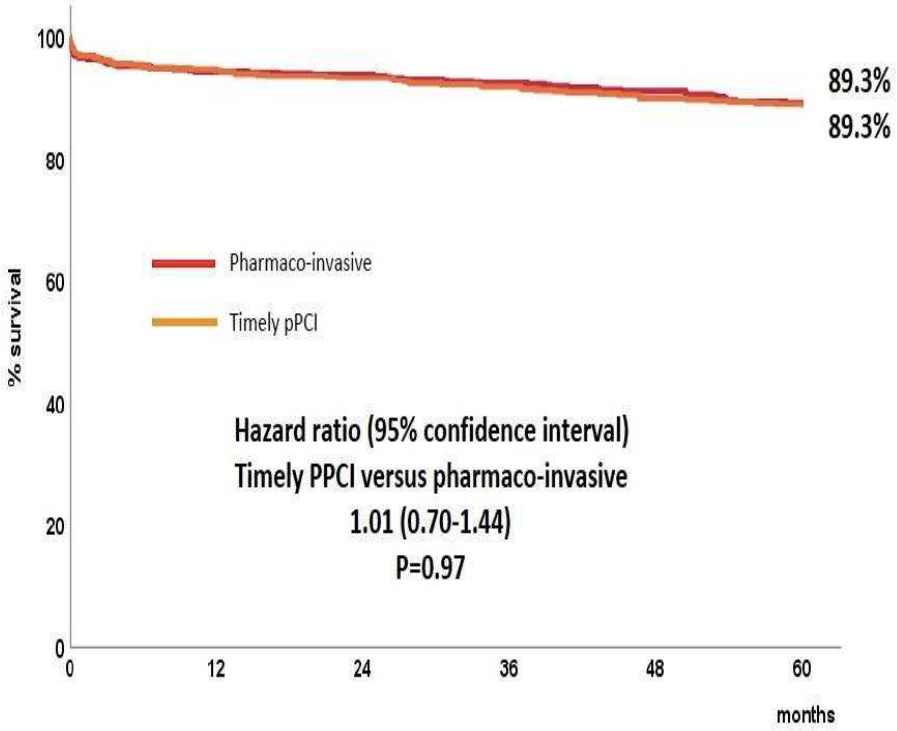
Number at risk						
Pharmaco-invasive	824	779	766	751	737	720
Timely PPCI	1288	1212	1174	1140	1096	1066
Late PPCI	830	749	724	689	648	626

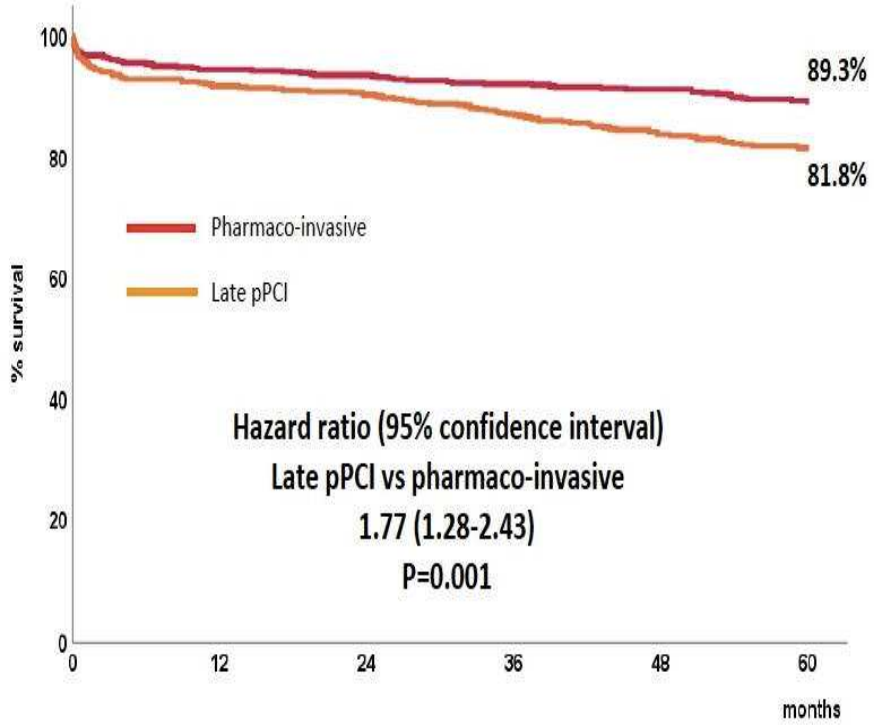
FAST-MI : Survie sans événements à 5 ans selon le type de reperfusion



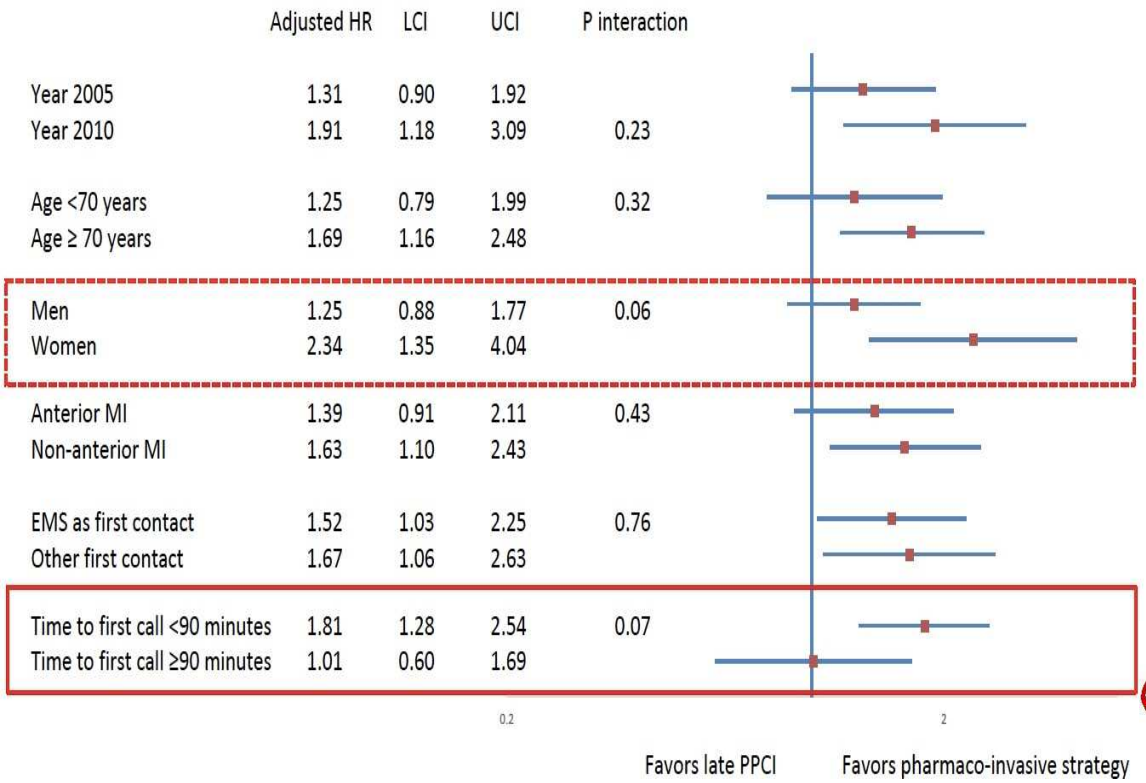
Number at risk						
Pharmaco-invasive	679	614	604	588	580	566
Timely PPCI	1013	944	905	874	836	817
Late PPCI	675	579	563	531	496	478

FAST-MI : Survie ajustée à 5 ans selon le type de reperfusion





FAST-MI : Analyses de sous groupe

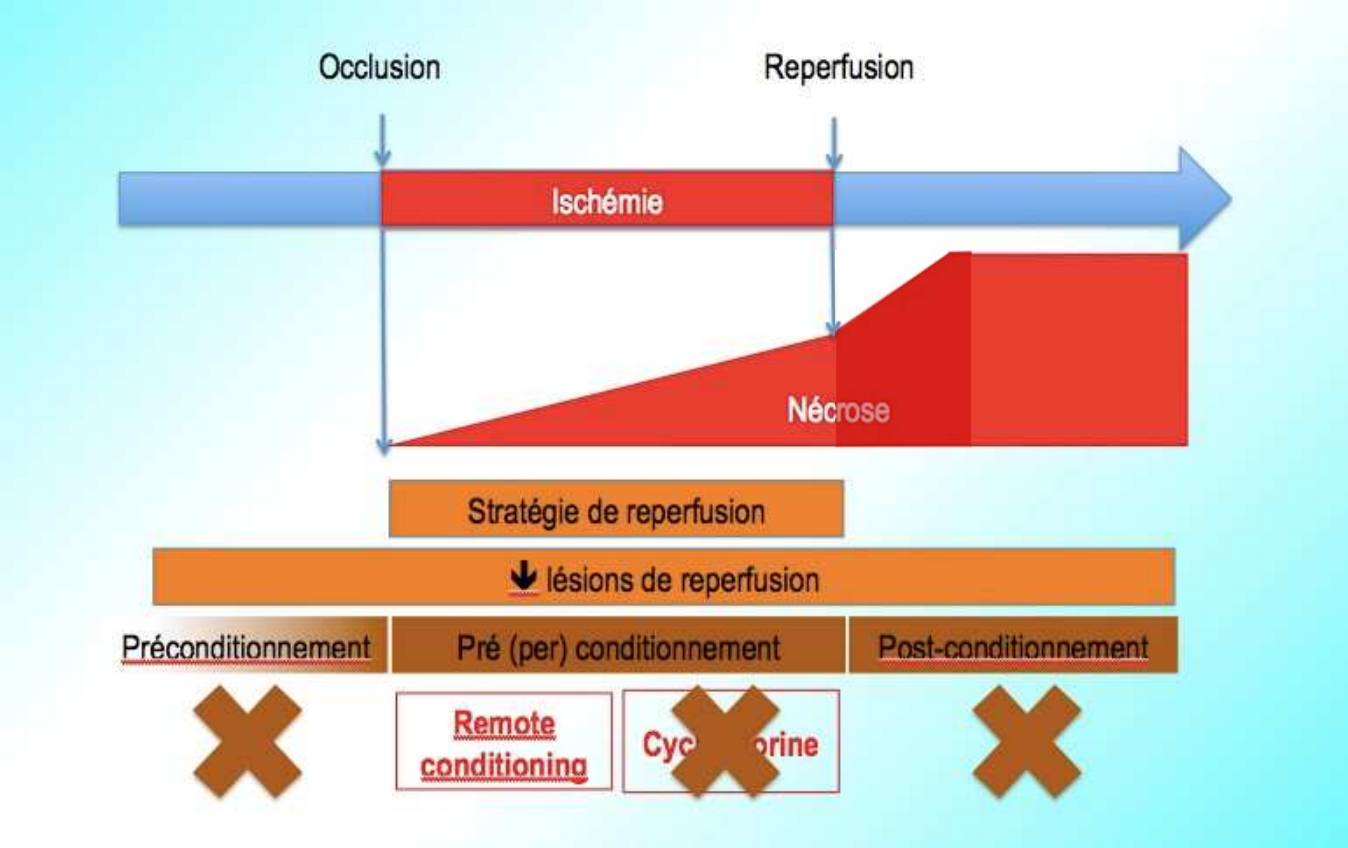


Délais début de douleur / Délai porte-porte*	< 3h	3h à 12h
< 60 min	ANGIOPLASTIE	ANGIOPLASTIE
≥ 60 min (ou doute sur précision du délai)	THROMBOLYSE	ANGIOPLASTIE**

* Délai porte-porte = délai entre le diagnostic par le médecin pouvant thrombolyser et l'arrivée devant la salle de cardiologie interventionnelle.

** Envisager une fibrinolyse pour les patients très éloignés des salles de cardiologie interventionnelle, avec des infarctus larges.

CONDITIONNEMMENT ISCHEMIQUE



CONDI2-REMOTE

Enrollment 5401

	Control	RIC
Allocation	2701	2700
Follow-up	2662	2671
Analysis -intention-to-treat	2569	2546

Excluded on arrival to hospital

Lost to follow-up

5 min.	5 min.	5 min.	5 min.	5 min.	5 min.	5 min.
Inflation	Deflation	Inflation	Deflation	Inflation	Deflation	Inflation

Lancet 2019;3941515

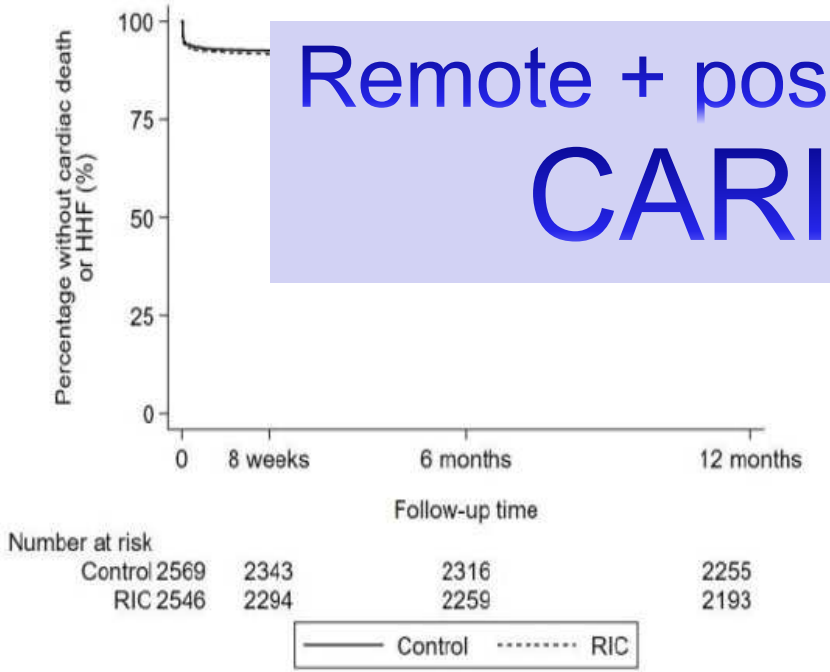
Result: Primary end point

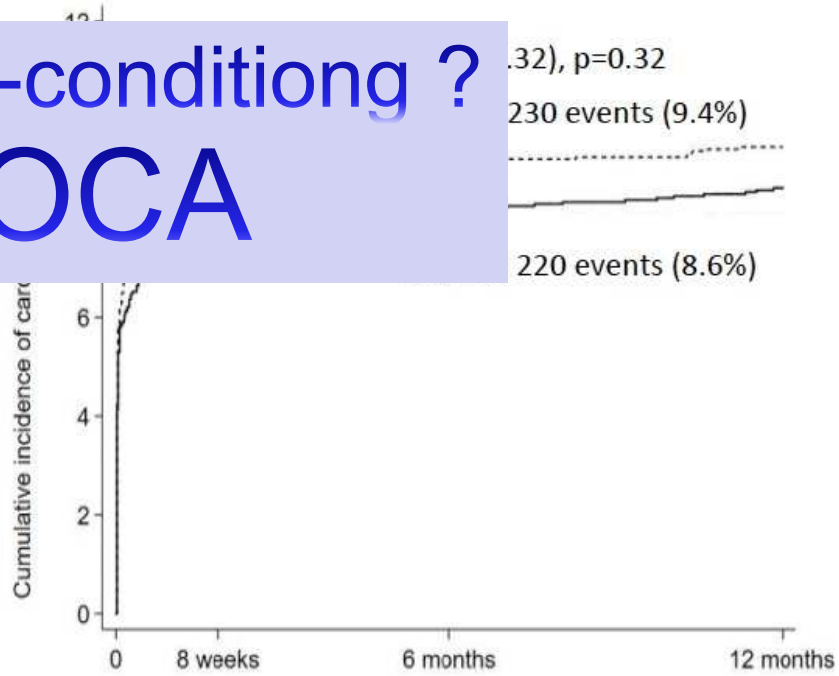
ERIC-PPCI

Combined EP: cumulative Incidence of Cardiac Death or HHF at 12 Months

Remote + post-conditiong ?

CARIOCA

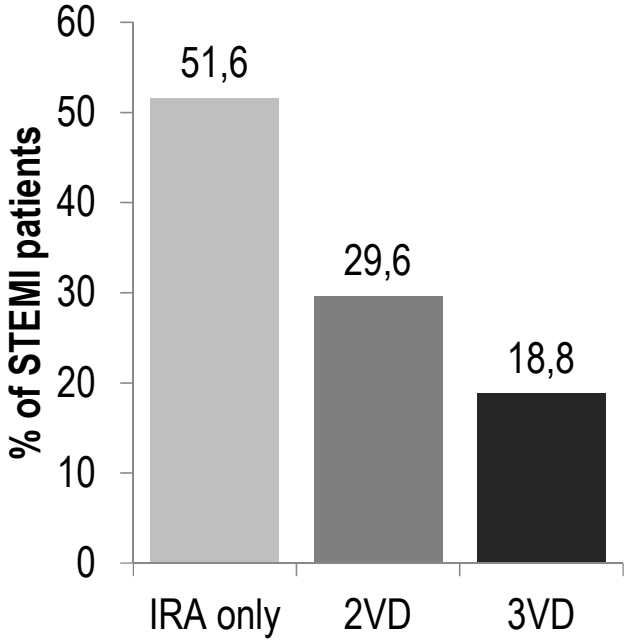


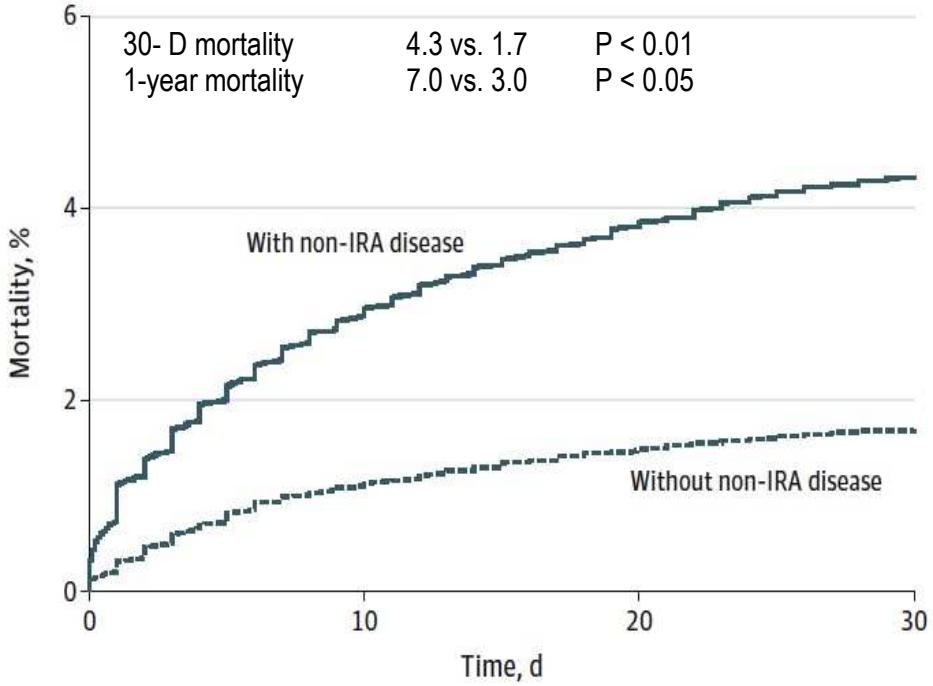


Lancet 2019;3941515

Revascularisation du patient pluri-tronculaire dans les SCA

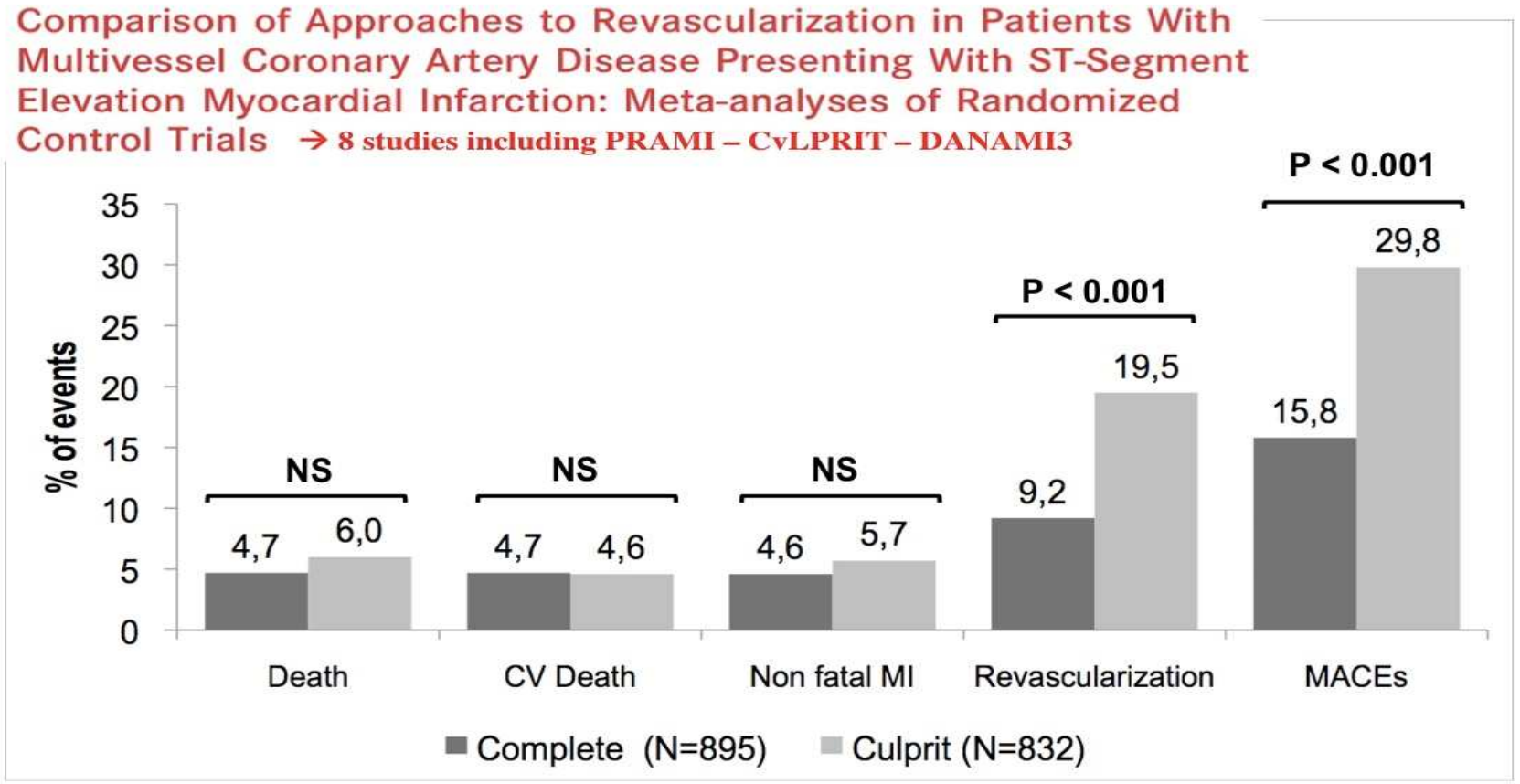
Retrospective study pooled from 8 RCTs = 28 283 pts





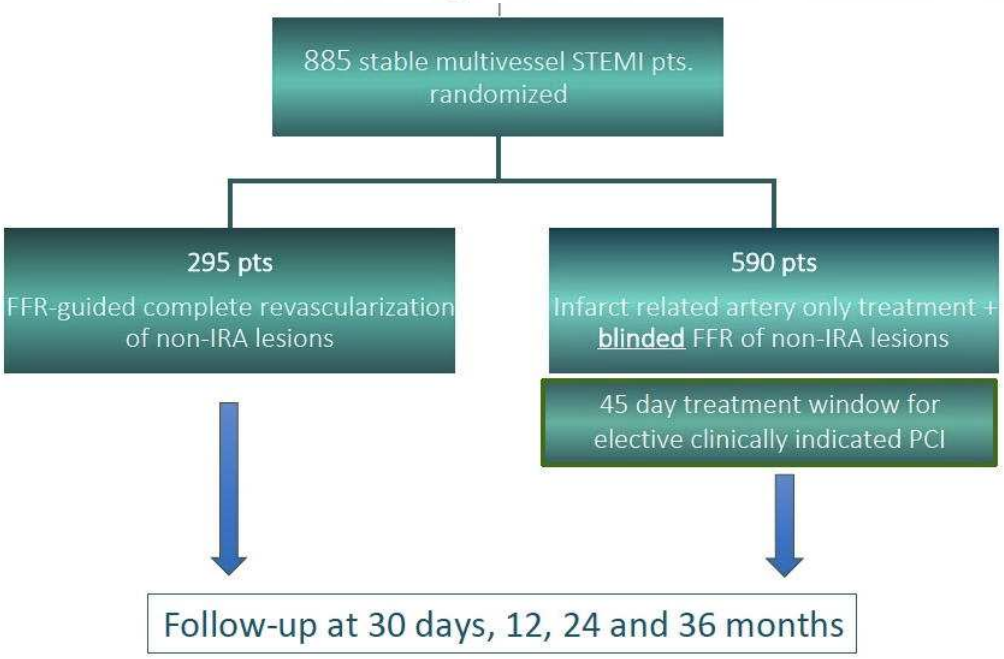
Park & al. JAMA 2014;312.:2019-2027

Revascularisation du patient pluri-tronculaire dans les SCA



Compare-Acute à 3 ans

FFR guided acute complete revascularization *versus* culprit lesion only treatment in patients presenting with STEMI and multivessel disease; final 3-year outcome data from Compare-Acute trial

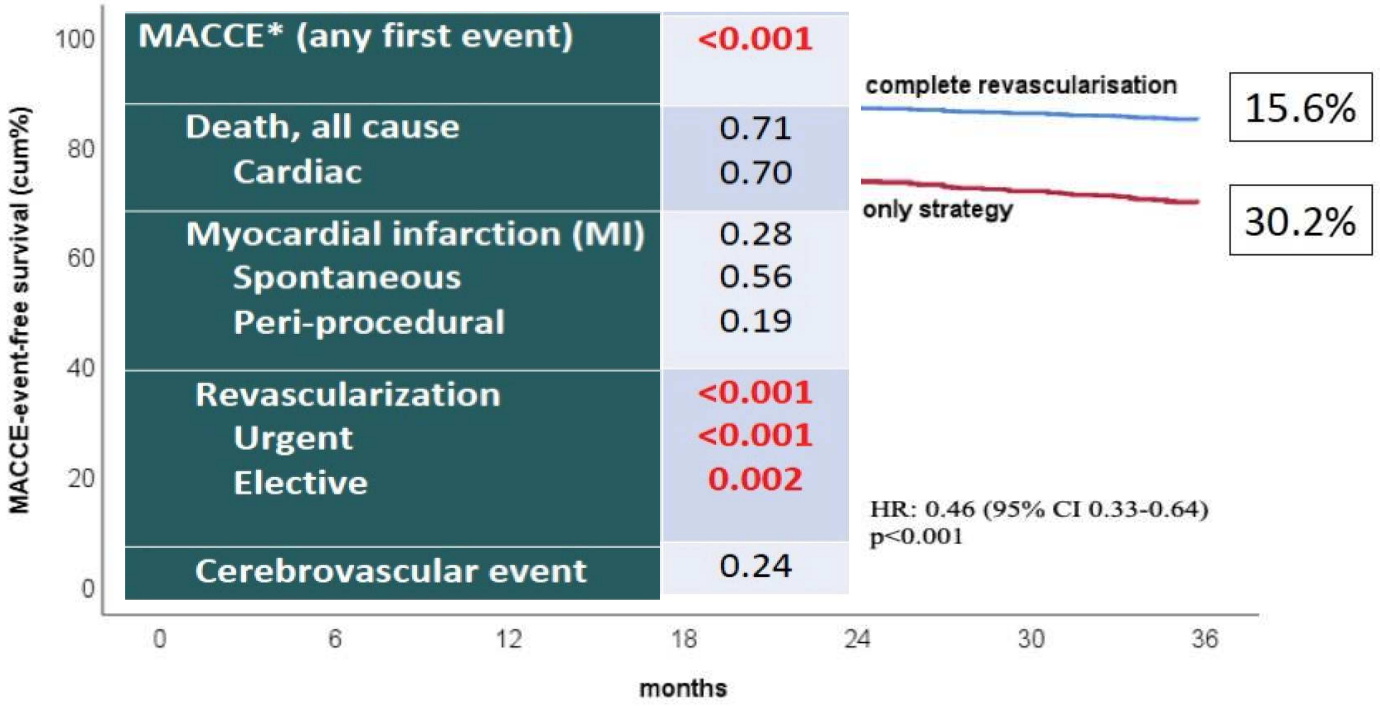


During index PCI procedure	136/163 (83.4)
Delayed during index hospitalization‡	27/163 (16.6)

NEJM 2017;376:1244

Confirmation des résultats à 3 ans de Compare-Acute

Primary endpoint MACCE :
Cardiac death, Myocardial Infarction, Revascularization & Stroke

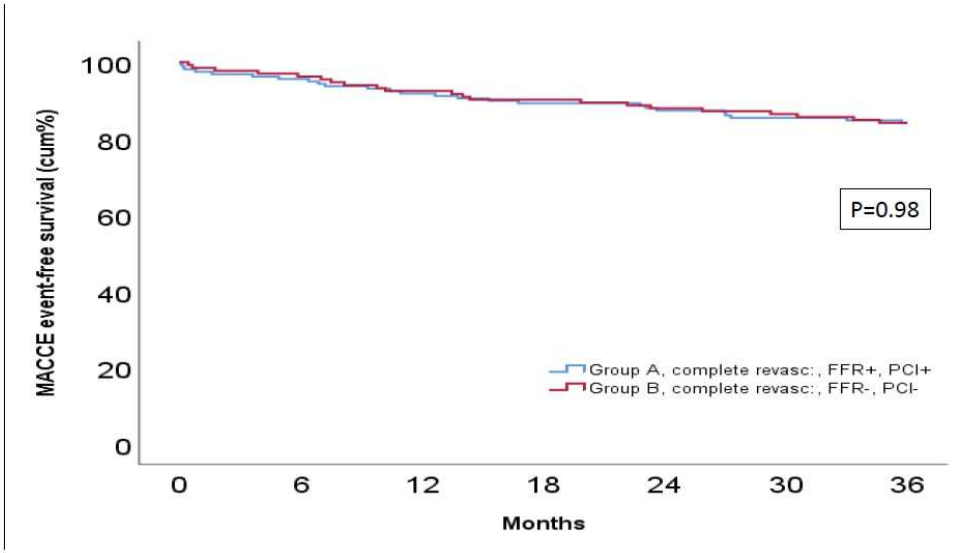


NEJM 2017;376:1244

Innocuité des sténoses FFR négative

Subgroup analysis

FFR guided subgroup A: FFR+/PCI+ *versus* subgroup B: FFR-/PCI-



- FFR-negative lesions (>0.80) in non-infarct arteries have a benign follow-up

NEJM 2017;376:1244

COMPLETE : Design

4041 patients ACT I^{aire} pour STEMI et pluritronculaires
(77% bitronculaires – 23% tritronculaires)

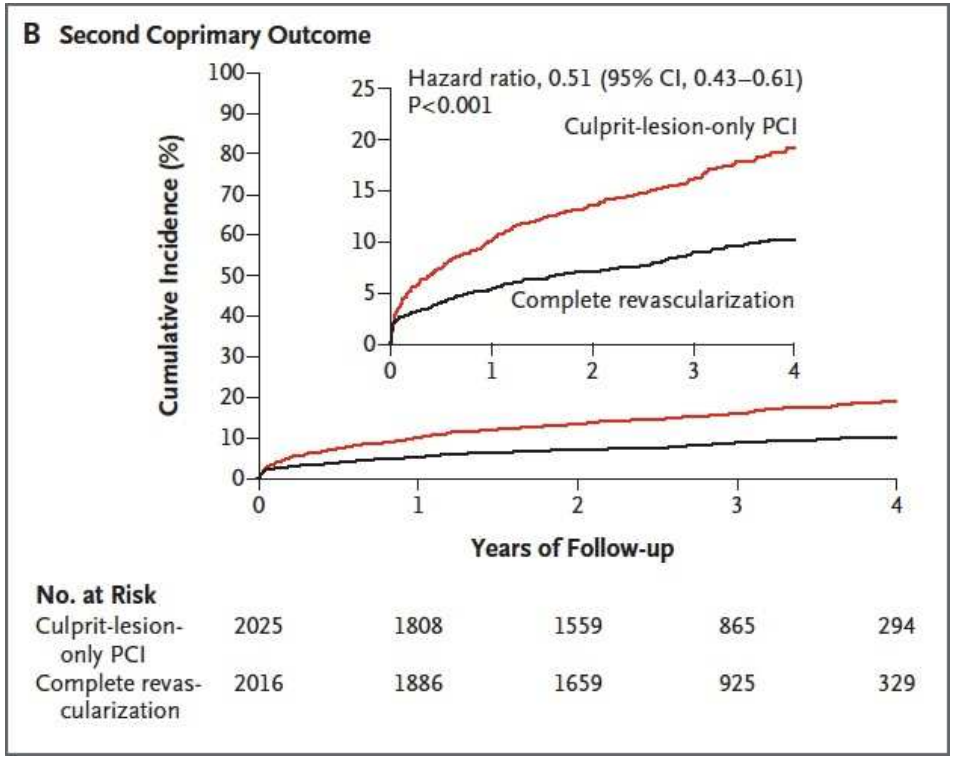
- CULPRIT-ONLY
- COMPLETE STAGED REVASC.
  - Lésions > 70%
  - Lésions 50-70% avec FFR < 0.80
    - Strate 1 (n=1285) Index hosp. Δ = 1 j [1-3]
    - Strate 2 (n=596) Delayed hosp. Δ = 23 j [12-33]

No./total no. of lesions (%)		
50–69%, with fractional flow reserve <0.80	21/2612 (0.8)	16/2576 (0.6)
70–79%	1078/2612 (41.3)	1162/2576 (45.1)
80–89%	875/2612 (33.5)	839/2576 (32.6)
90–99%	583/2612 (22.3)	508/2576 (19.7)
100%	55/2612 (2.1)	51/2576 (2.0)

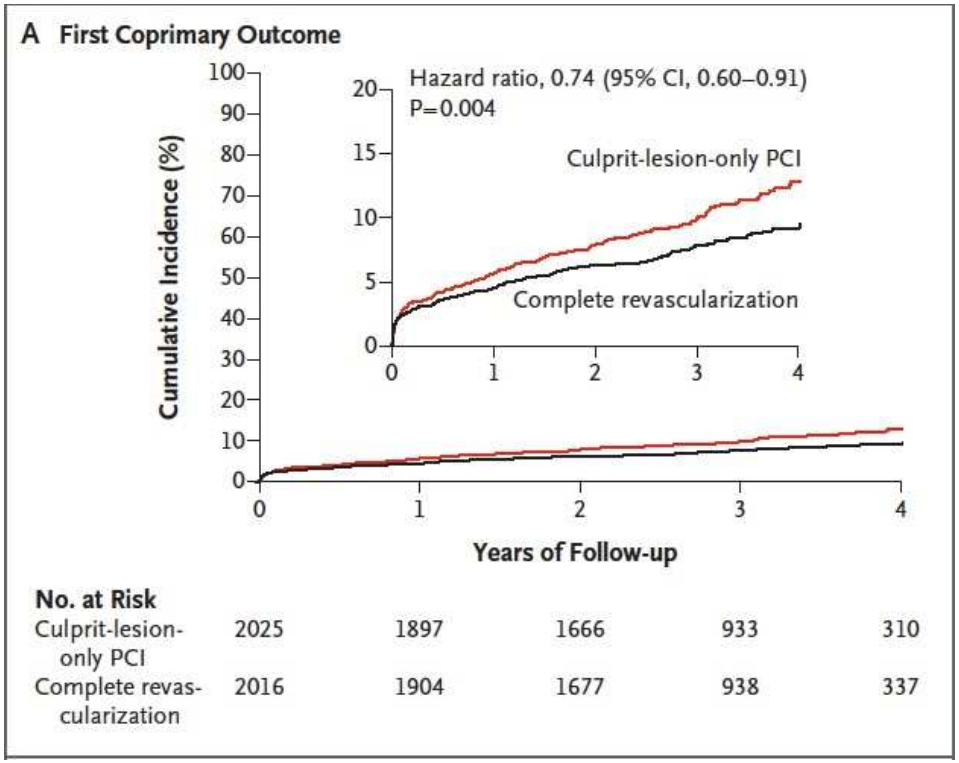
NEJM 2019:381:1411

COMPLETE : Résultats

† + IDM + Revascularisation



† + IDM



NEJM 2019:381:1411

COMPLETE

Outcome	Complete Revascularization (N=2016)		Culprit-Lesion-Only PCI (N=2025)		Hazard Ratio (95% CI)	P Value
	no. (%)	*% per person-yr*	*no. (%)*	*% per person-yr*		
Coprimary outcomes						
Cardiovascular death or myocardial infarction	158 (7.8)	2.7	213 (10.5)	3.7	0.74 (0.60–0.91)	0.004
Cardiovascular death, myocardial infarction, or ischemia-driven revascularization	179 (8.9)	3.1	339 (16.7)	6.2	0.51 (0.43–0.61)	<0.001
Key secondary outcome						
Cardiovascular death, myocardial infarction, ischemia-driven revascularization, unstable angina, or NYHA class IV heart failure	272 (13.5)	4.9	426 (21.0)	8.1	0.62 (0.53–0.72)	
Other secondary outcomes						
Myocardial infarction	109 (5.4)	1.9	160 (7.9)	2.8	0.68 (0.53–0.86)	
Ischemia-driven revascularization	29 (1.4)	0.5	160 (7.9)	2.8	0.18 (0.12–0.26)	
Unstable angina	70 (3.5)	1.2	130 (6.4)	2.2	0.53 (0.40–0.71)	
Death from cardiovascular causes	59 (2.9)	1.0	64 (3.2)	1.0	0.93 (0.65–1.32)	
Death from any cause	96 (4.8)	1.6	106 (5.2)	1.7	0.91 (0.69–1.20)	

NEJM 2019:381:1411

COMPLETE : Timing de revascularisation complète

Subgroup	First Coprimary Outcome			
	Complete revascularization	Culprit-lesion-only PCI	Hazard ratio (95% CI)	P value for interaction
	no. of events/ total no. of patients (% per person-yr)			
Overall	158/2016 (2.7)	213/2025 (3.7)	0.74 (0.60–0.91)	
Intended timing of nonculprit-lesion PCI				0.62
During index hospitalization	101/1353 (2.7)	130/1349 (3.5)	0.77 (0.59–1.00)	
After hospital discharge	57/663 (2.7)	83/676 (3.9)	0.69 (0.49–0.97)	

NEJM 2019:381:1411

COMPLETE…ment inadaptée ?

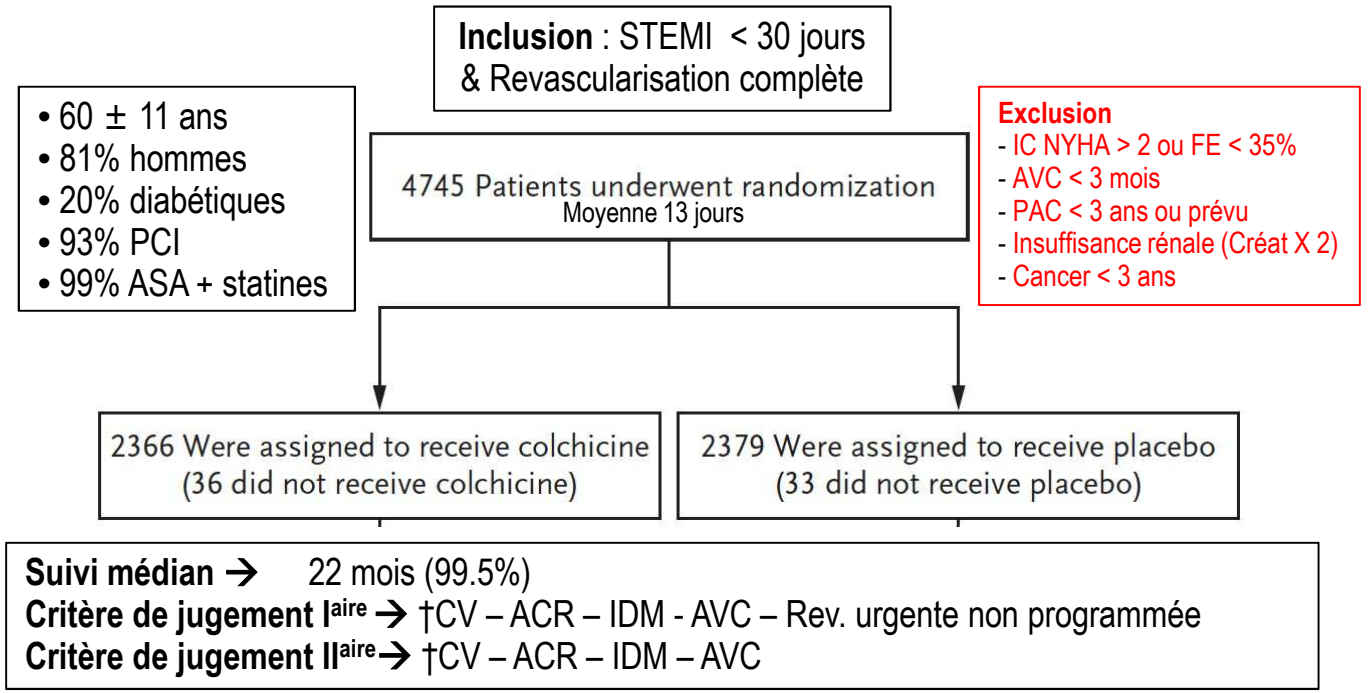
Patients who were randomly assigned to the complete-revascularization strategy were to have routine staged PCI (i.e., PCI during a procedure separate from the index PCI procedure for STEMI) of all suitable nonculprit lesions, regardless of whether there were clinical symptoms or there was evidence of ischemia. Investigators specified

Patients who were randomly assigned to the culprit-lesion-only PCI strategy received guideline-based medical therapy with no further revascularization, regardless of whether there was evidence of ischemia on noninvasive testing.

Cross over → revascularisation uniquement si
Re-IDM, choc, IC réfractaire, angor réfractaire + ischémie documentée

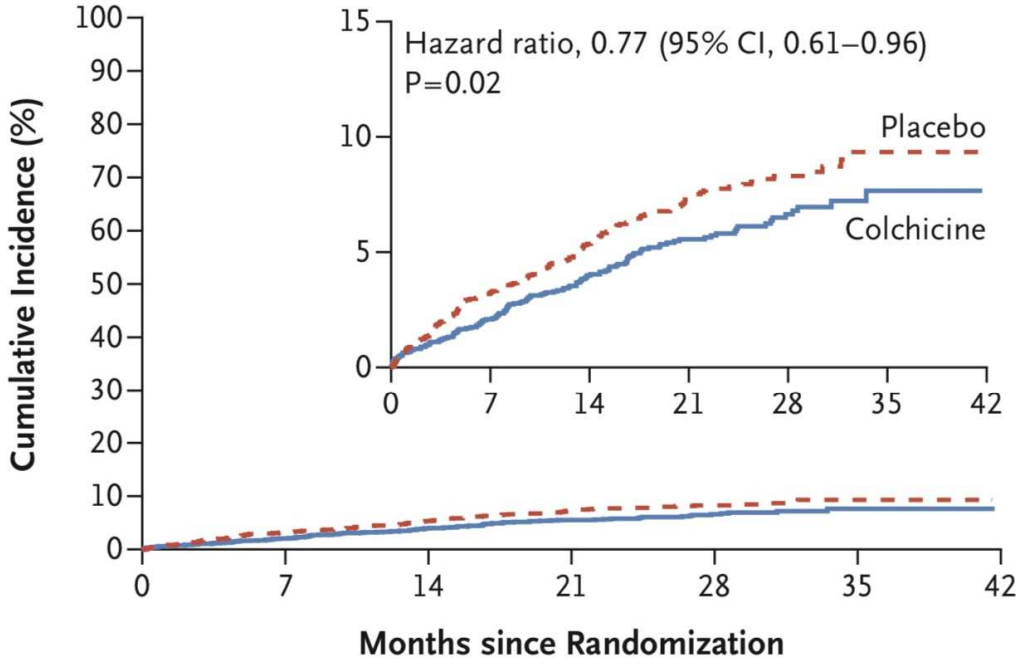
NEJM 2019:381:1411

COLCOT : Colchicine après STEMI



NEJM 2019:online pre-print

COLCOT : Résultats



No. at Risk							
Placebo	2379	2261	1854	1224	622	144	0
Colchicine	2366	2284	1868	1230	628	153	0

NEJM 2019:online pre-print

COLCOT : Résultats

Efficacité

End Point	Colchicine (N=2366)	Placebo (N=2379)	Hazard Ratio (95% CI)
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)
Components of primary end point			
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)
Urgent hospitalization for angina revascularization	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)
Secondary composite end point‡	111 (4.7)	130 (5.5)	0.85 (0.66–1.10)
Death	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59–1.46)

NEJM 2019:online pre-print

COLCOT : Résultats

Sécurité

Event	Colchicine (N=2330)	Placebo (N=2346)	P Value
	number of patients (percent)		
Any related adverse event†	372 (16.0)	371 (15.8)	0.89
Adverse events			
Gastrointestinal event	408 (17.5)	414 (17.6)	0.90
Diarrhea	225 (9.7)	208 (8.9)	0.35
Nausea	43 (1.8)	24 (1.0)	0.02
Flatulence	15 (0.6)	5 (0.2)	0.02
Gastrointestinal hemorrhage	7 (0.3)	5 (0.2)	0.56
Anemia	14 (0.6)	10 (0.4)	0.40
Leukopenia	2 (0.1)	3 (0.1)	0.66
Thrombocytopenia	3 (0.1)	7 (0.3)	0.21
Serious adverse events			
Any serious adverse event‡	383 (16.4)	404 (17.2)	0.47
Gastrointestinal event	46 (2.0)	36 (1.5)	0.25
Infection	51 (2.2)	38 (1.6)	0.15
Pneumonia	21 (0.9)	9 (0.4)	0.03

NEJM 2019:online pre-print

COLCOT – Sous-groupes

Subgroup	Colchicine	Placebo	Hazard ratio (95% CI)
	no. of patients with event/total no. of patients (%)		
All patients	131/2366 (5.5%)	170/2379 (7.1%)	0.77 (0.61-0.96)
Smoking			
Non-smoker	47/787 (6.0%)	52/797 (6.5%)	0.90 (0.61; 1.34)
Previous smoker	46/871 (5.3%)	77/872 (8.8%)	0.59 (0.41; 0.85)
Active smoker	38/708 (5.4%)	41/708 (5.8%)	0.93 (0.60; 1.44)
History of diabetes			
Yes	40/462 (8.7%)	65/497 (13.1%)	0.65 (0.44; 0.96)
No	91/1904 (4.8%)	105/1882 (5.6%)	0.85 (0.64; 1.13)
History of hypertension			
Yes	83/1185 (7.0%)	112/1236 (9.1%)	0.76 (0.57; 1.01)
No	48/1181 (4.1%)	58/1143 (5.1%)	0.80 (0.54; 1.17)
Prior MI			
Yes	46/370 (12.4%)	47/397 (11.8%)	1.05 (0.70; 1.58)
No	85/1996 (4.3%)	123/1982 (6.2%)	0.68 (0.51; 0.89)
Prior PCI or CABG			
Yes	48/419 (11.5%)	57/447 (12.8%)	0.91 (0.62; 1.34)
No	83/1947 (4.3%)	113/1932 (5.8%)	0.72 (0.54; 0.95)
Prior stroke or TIA			
Yes	8/55 (14.5%)	9/67 (13.4%)	1.09 (0.42; 2.82)
No	123/2311 (5.3%)	161/2312 (7.0%)	0.76 (0.60; 0.96)
Sex‡			
Male	94/1894 (5.0%)	135/1942 (7.0%)	0.70 (0.54; 0.91)
Female	37/472 (7.8%)	35/437 (8.0%)	0.99 (0.63; 1.58)

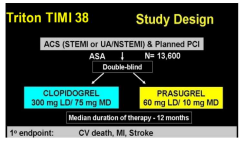
Passé de tabagisme

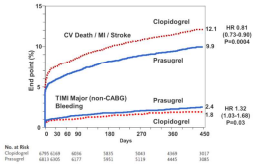
Diabétique

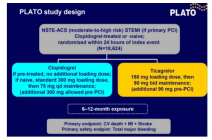
Homme

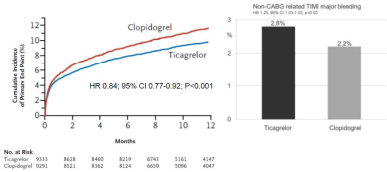
P2Y12 dans les SCA

1. **P2Y12i de 2nde génération > Clopidogrel**
- *PLATO*
- *TRITON-TIMI 38*









2. **Prétraitement des SCA non-ST+**
- Effet délétère du préT par le Prasugrel *(ACCOAST)*
- Pas d'étude pré vs. post-TTT avec le Ticagrelor

3. **Pré-traitement dans les SCA- ST**
- La règle depuis le Clopidogrel *(CLARITY & COMMIT)*
- Post = pré-traitement par Ticagrelor dans les SCA ST+ pris précocement *(ATLANTIC)*

4. **Absence de comparaison directe Ticagrelor vs. Prasugrel dans les SCA**

ISAR REACT 5 : Ticagrelor vs. Prasugrel dans les SCA

Aim

- Head-to-head comparison of a Ticagrelor- versus a Prasugrel-based strategy in ACS patients with and without ST-segment elevation in terms of one-year clinical outcomes

Design

- Investigator-initiated, randomized, multicenter, open-label

  Financement publique *(German Center for Cardiovascular Research & Deutsches Herzzentrum München)*

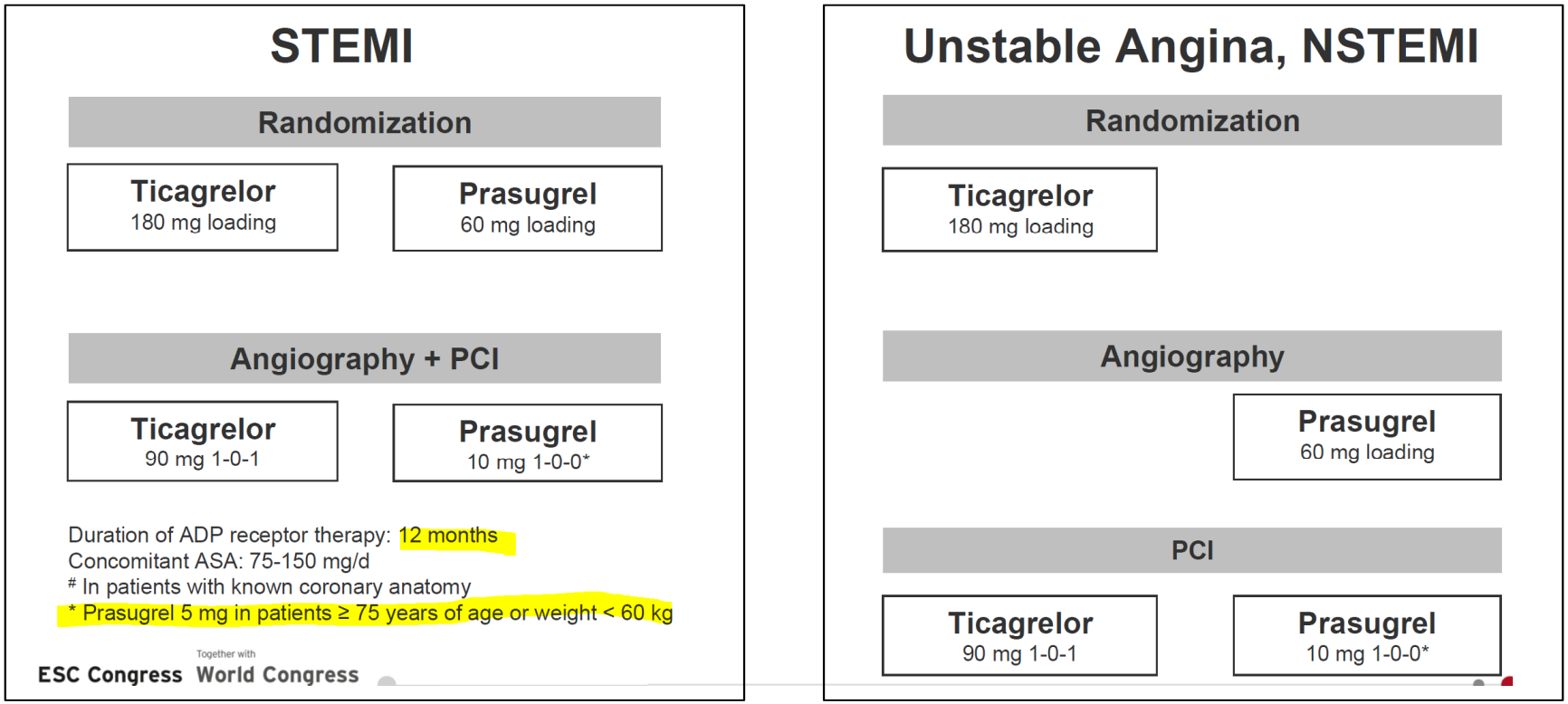
Hypothèse

• Supériorité du ticagrelor sur le critère de jugement principal → mortalité + infarctus + AVC à 1 an.

4018 patients randomisés

NEJM 2019;381:1524

ISAR REACT 5 : Stratégie PLATO vs. Stratégie TRITON



NEJM 2019;381:1524

ISAR REACT 5 : Population

- 64.5 ans, 76% d'hommes
- Diabétiques : 22%
- NSTEMI : 46% - STEMI 44% - UA 10%
- PCI : 85% - CABG 2% - MED 13%
- Traitement de sortie optimisé :
  - ASA 95 %
  - P2Y12 alloué 81 %
  - ßbts 83 %
  - IEC 85 %
  - Statines 93 %
- F-UP : 97.8% - 1an

- **Critères d'exclusion**
- Tout antécédent intra-cranien
- Saignement actif
- Risque hémorragique élevé
- Thrombolyse < 24 heures
- IR dialysée

Pour le prasugrel 10 mg
- âge > 75 ans
- et/ou poids < 60 kg

NEJM 2019;381:1524

ISAR REACT 5 : Résultats

The NEW ENGLAND JOURNAL of MEDICINE

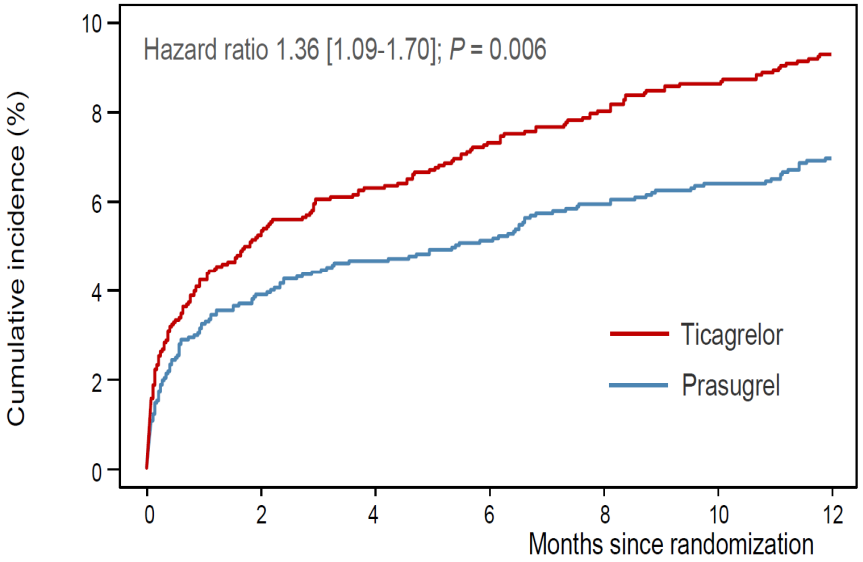
ORIGINAL ARTICLE

Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

An unexpected finding was that the risk of ischemic events (the composite of death, myocardial infarction, or stroke) at 1 year after randomization in the ISAR-REACT 5 trial was significantly lower in the prasugrel group than in the ticagrelor group.

NEJM 2019;381:1524

ISAR REACT 5 : Critère de jugement principal († - IDM – AVC)



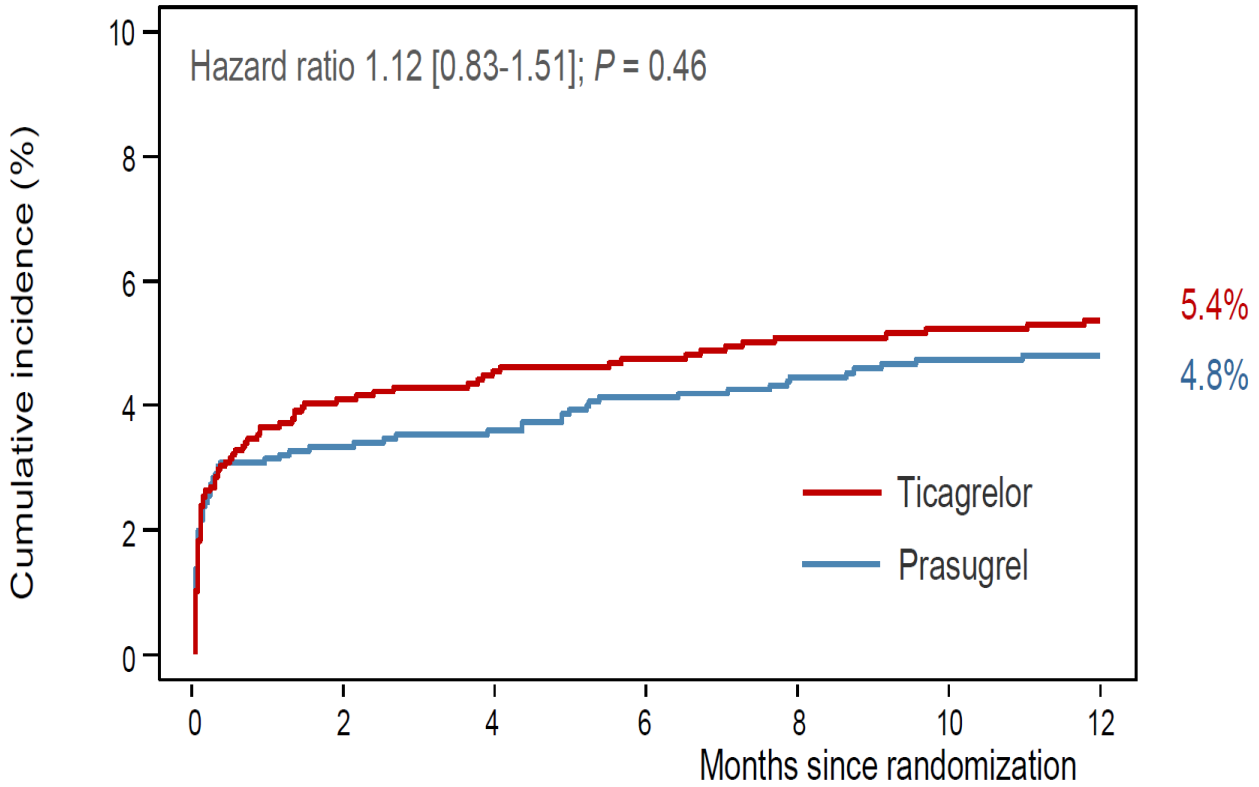
9.3%

6.9%

End Point	Ticagrelor Group (N = 2012)	Prasugrel Group (N = 2006)	Hazard Ratio (95% CI)
Death — no. (%)			
From any cause	90 (4.5)	73 (3.7)	1.23 (0.91–1.68)
From cardiovascular cause	63 (3.2)	59 (3.0)	
From noncardiovascular cause	27 (1.4)	14 (0.7)	
Myocardial infarction — no. (%)†	96 (4.8)	60 (3.0)	1.63 (1.18–2.25)
Stroke			
Any — no. (%)	22 (1.1)	19 (1.0)	1.17 (0.63–2.15)
Ischemic — no.	16	17	
Hemorrhagic — no.	6	2	
stent thrombosis — no. (%)	26 (1.3)	20 (1.0)	1.30 (0.72–2.33)

NEJM 2019;381:1524

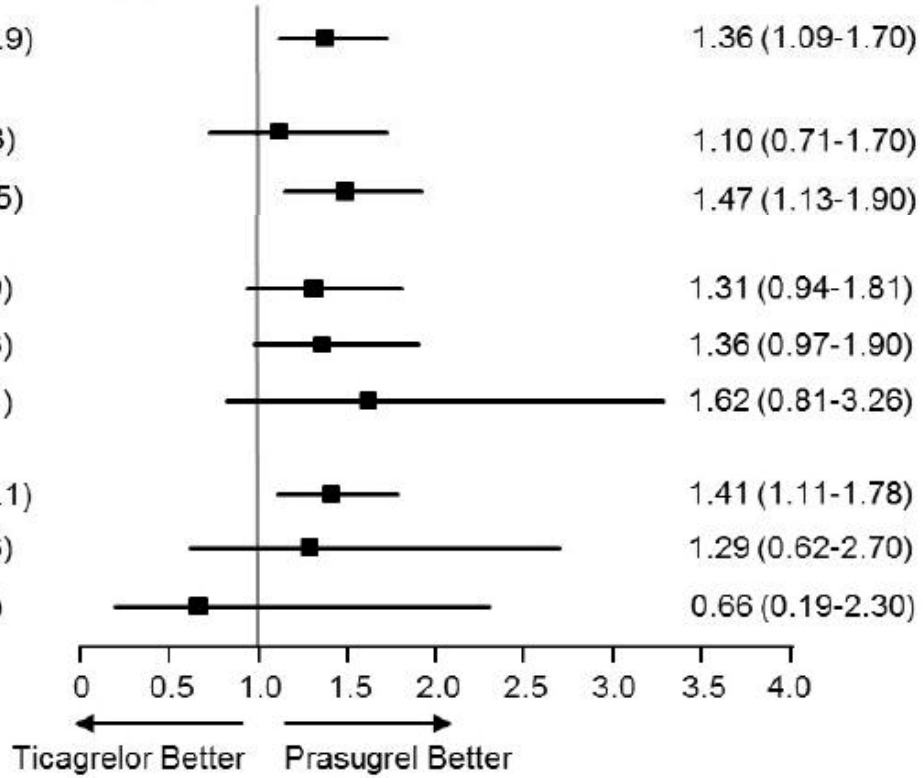
ISAR REACT 5 : Critère de sécurité principal (BARC 3-5 bleedings)



NEJM 2019;381:1524

ISAR REACT 5 : Sous-groupes

Subgroup	Ticagrelor	Prasugrel	Hazard Ratio (95% CI)
	no. of patients with event/total no. of patients (%)		
Overall	184/2012 (9.3)	137/2006 (6.9)	1.36 (1.09-1.70)
Sex			
Female	42/478 (8.9)	39/478 (8.3)	1.10 (0.71-1.70)
Male	142/1534 (9.4)	98/1528 (6.5)	1.47 (1.13-1.90)
Clinical Presentation			
STEMI	83/833 (10.1)	64/820 (7.9)	1.31 (0.94-1.81)
NSTEMI	81/930 (8.8)	60/925 (6.6)	1.36 (0.97-1.90)
Unstable Angina	20/249 (8.2)	13/261 (5.1)	1.62 (0.81-3.26)
Treatment Strategy			
PCI	162/1676 (9.8)	120/1701 (7.1)	1.41 (1.11-1.78)
Conservative	17/285 (6.1)	12/268 (4.6)	1.29 (0.62-2.70)
CABG	5/47 (10.6)	5/36 (13.9)	0.66 (0.19-2.30)



NEJM 2019;381:1524

ISAR REACT 5 : Conclusions

CONCLUSIONS

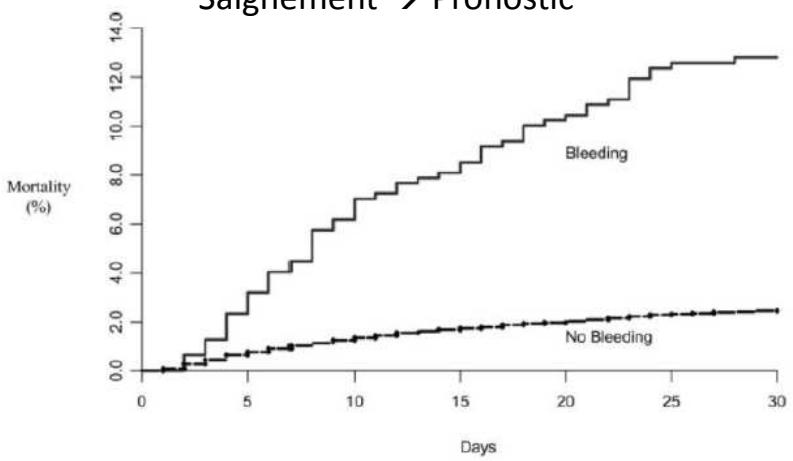
Among patients who presented with acute coronary syndromes with or without ST-segment elevation, the incidence of death, myocardial infarction, or stroke was significantly lower among those who received prasugrel than among those who received ticagrelor, and the incidence of major bleeding was not significantly different between the two groups. (Funded by the German Center for Cardiovascular Research and Deutsches Herzzentrum München; ISAR-REACT 5 ClinicalTrials.gov number, NCT01944800.)

Une pierre de plus en faveur du non pré-traitement des SCA non-ST+

NEJM 2019;381:1524

Popular-Age Trial : Optimal P2Y12 inhibitors > 70 years in NSTE-ACS

Saignement → Pronostic



- Prasugrel et Ticagrelor vs. Clopidogrel
  - Dimininution du risque ischémique
  - Sur-risque hémorragique
- Sous représentation des patients > 75 ans
  - 13 % dans TRITON
  - 15 % dans PLATO
  - 24 % dans ISAR-REACT 5

Eikelboom et al. Circulation. 2006;114:774-782 2. Roy et al. AJC 2008;102:1614-1617

Hypothesis

Clopidogrel is superior in reducing bleeding risk and non-inferior in net clinical benefit compared to ticagrelor/prasugrel in patients of 70 years or older with non-ST-elevation acute coronary syndrome

Popular-Age Trial : Optimal P2Y12 inhibitors > 70 years in NSTE-ACS

Essai randomisé ouvert
Financement publique
(Ministère Hollandais)

Inclusion criteria

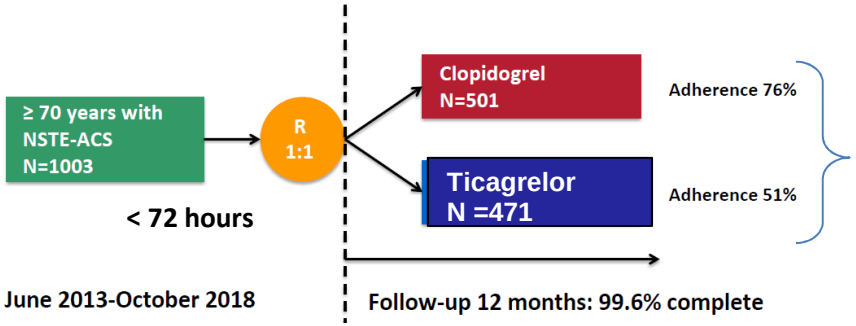
- Age ≥ 70 years — 77 [73 – 82]
- Admitted with NSTE-ACS

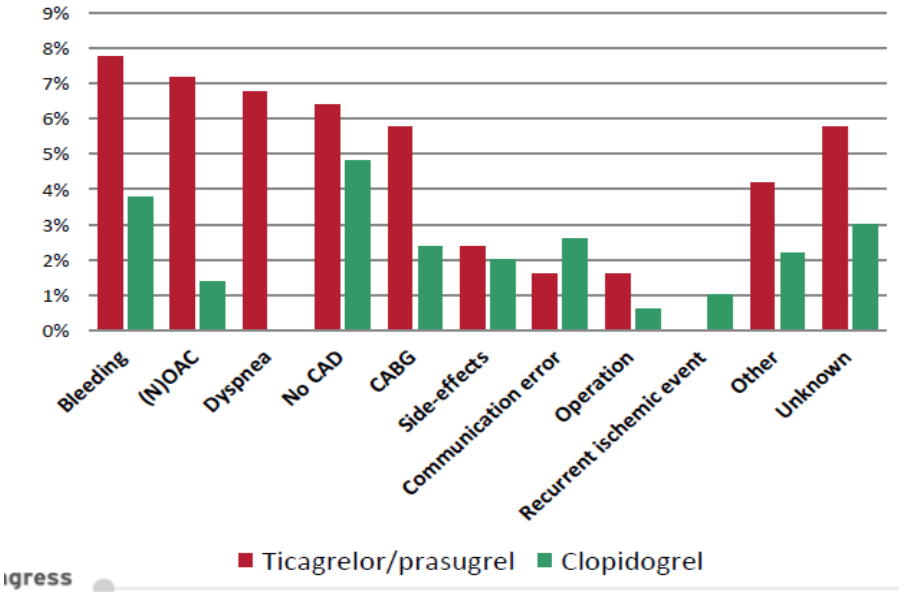
- 84 % NSTEMI
- 10 % UA

- 90 % coronarographie
- 48 % PCI
- 17 % CABG
- 35 % MEDICAL

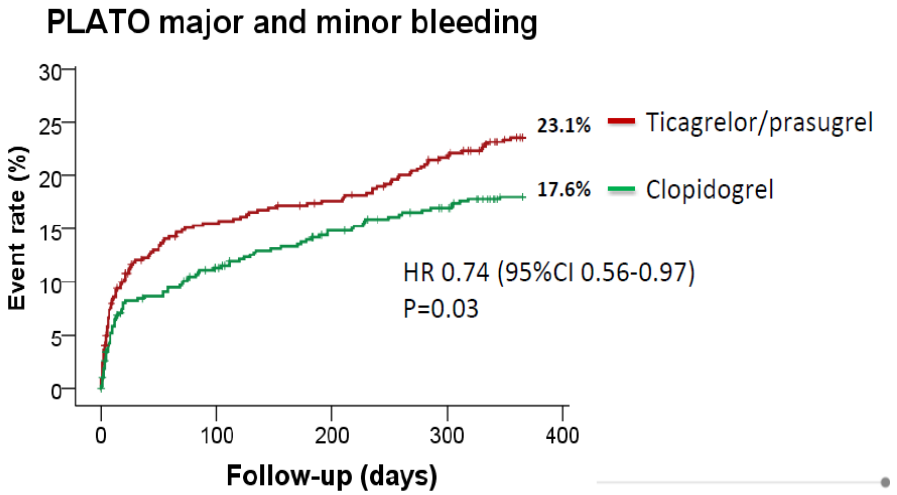
Key exclusion criteria

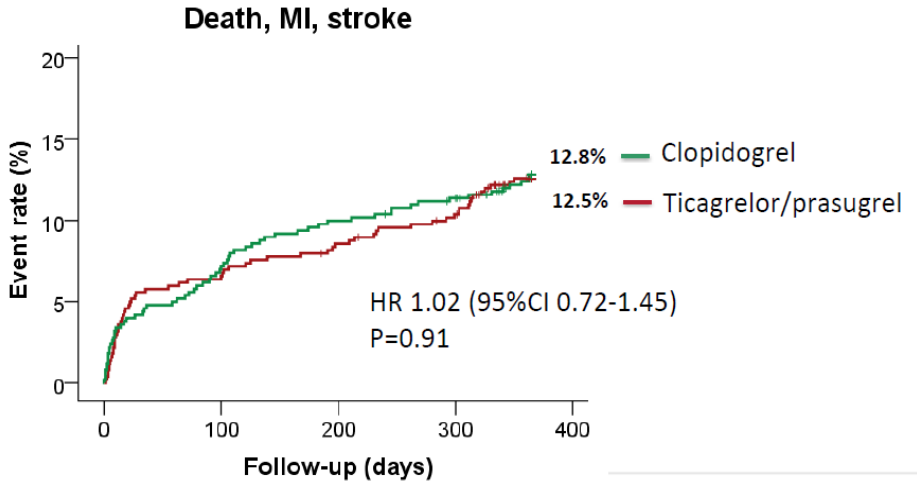
- Contraindication $P2Y_{12}$ inhibitors
- DAPT use prior to admission
- Indication for major surgery
- Life expectancy < 1 year



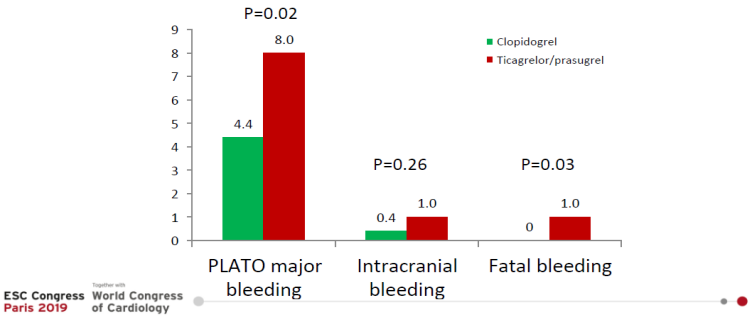


Popular-Age Trial : Optimal P2Y12 inhibitors > 70 years

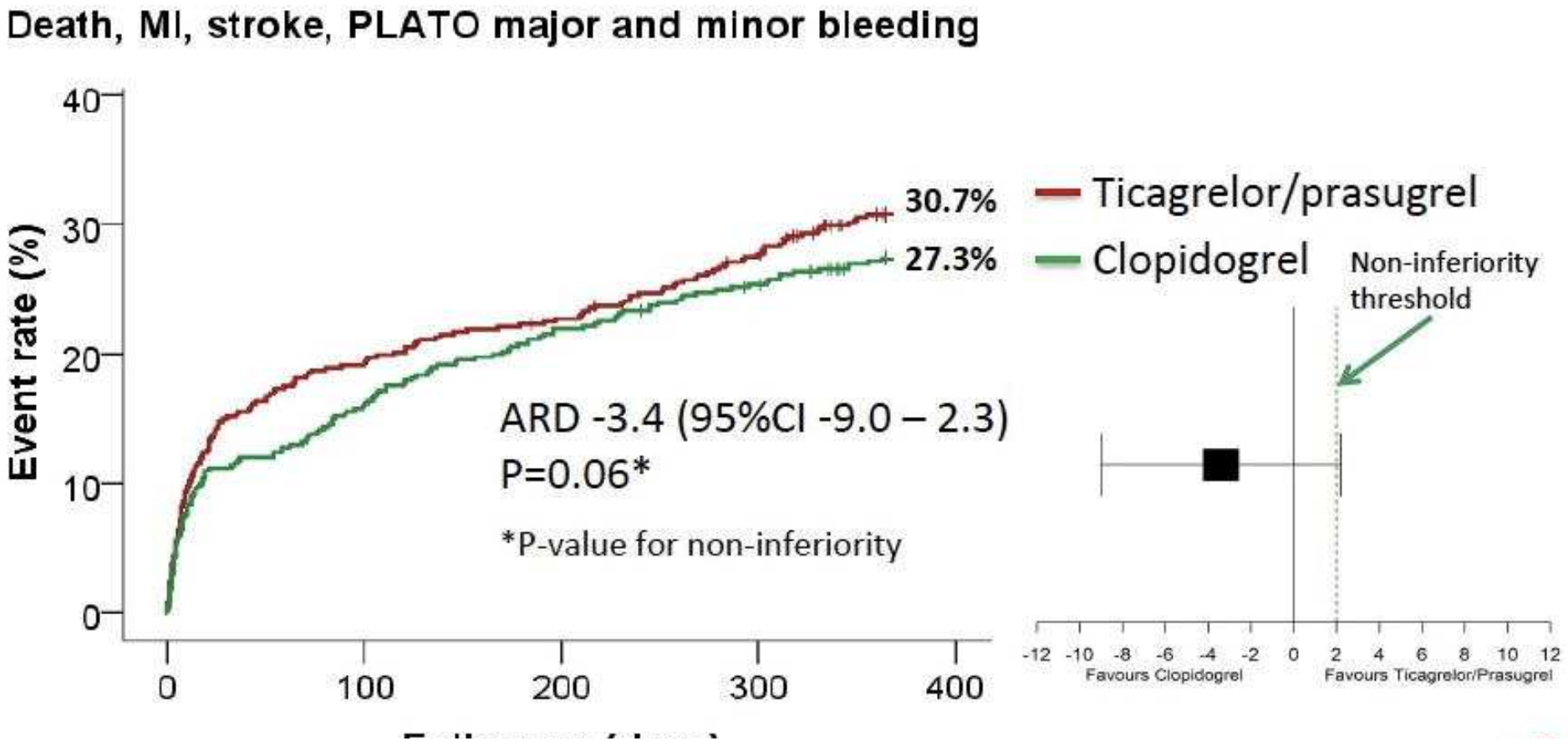




Secondary safety outcomes



Bénéfice clinique net



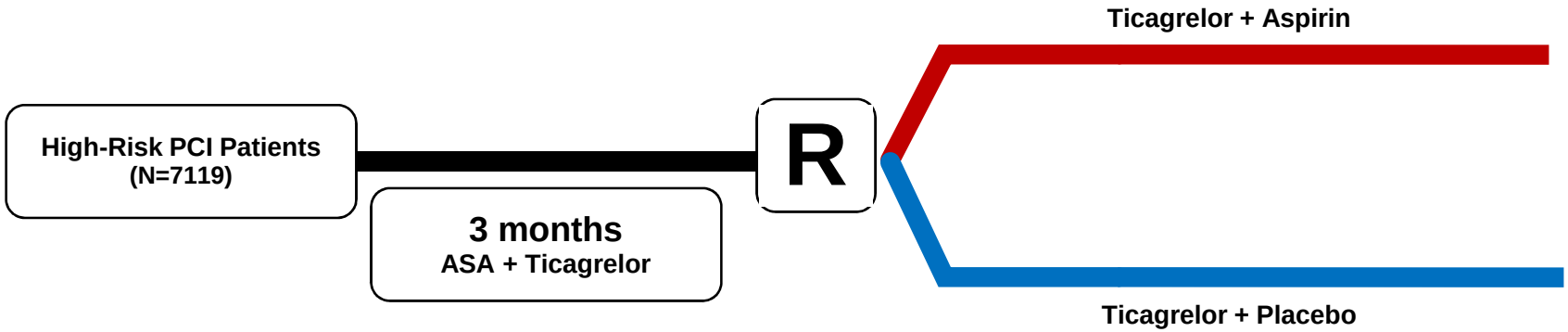
Conclusion

- Compared to ticagrelor/prasugrel in the POPular AGE trial we conclude:
  - Clopidogrel significantly less bleeding
  - Clopidogrel similar in preventing thrombotic events
- Therefore, we consider clopidogrel the preferred treatment in patients ≥ 70 years with NSTE-ACS

Take home message

- **La reperfusion précoce reste la seule arme efficace dans le STEMI**
  - → Thrombolysez !!
  - → Pas d'efficacité du conditionnement ischémique
- **Les lésions tritronculaires doivent être revascularisées « tôt »**
  - → Dans les 3 semaines suivent l'infarctus
  - → Pour limiter les MACE « durs » (Mortalité + IDM)
  - → FFR : rester pragmatique…
- **P2Y12 dans les SCA**
  - → Stratégie TRITON > PLATO sur les MACEs (IDM)
  - → SCA non ST+ : Clopidogrel+ ASA > 75 ans ? (ou Ticagrelor seul > 3 mois)?
- **Quelle place donner à la colchicine après STEMI ?**

TWILIGHT : Design



Primary Objective:

To determine the impact of SAPT (ticagrelor monotherapy) *versus* DAPT (ticagrelor plus aspirin) for 12 months in reducing **clinically relevant bleeding** (BARC 2, 3 or 5) among high-risk patients who have undergone successful PCI.

Secondary Objective:

To determine the impact of SAPT (ticagrelor monotherapy) *versus* DAPT (ticagrelor plus aspirin) for 12 months on **major ischemic adverse events** (all-cause death, non-fatal MI or stroke) among high-risk patients who have undergone successful PCI.

NEJM 2019;381:2032

TWILIGHT : Critères d'inclusion / Exclusion

Au moins un critère clinique + 1 critère angiographique

Clinical criteria

- Age ≥65 years
- Female gender
- Troponin positive ACS
- Established vascular disease (previous MI, documented PAD or CAD/PAD revasc)
- DM treated with medications or insulin
- CKD (eGFR <60ml/min/1.73m^2 or CrCl <60ml/min)

Angiographic criteria

- Multivessel CAD
- Target lesion requiring total stent length >30mm
- Thrombotic target lesion
- Bifurcation lesion(s) with Medina X,1,1 classification requiring ≥2 stents
- Left main (≥50%) or proximal LAD (≥70%) lesions
- Calcified target lesion(s) requiring atherectomy

Exclusion : STEMI, antécédent d'AVC, indication d'AOD/AVK (…)

NEJM 2019;381:2032

TWILIGHT : Caractéristiques cliniques

Variable	Tica + Placebo (N = 3555)	Tica + Aspirin (N = 3564)
Age, years [Mean ± SD]	65.2 ± 10.3	65.1 ± 10.4
Diabetes Mellitus	37.1%	36.5%
Insulin requiring	9.4%	10.5%
Chronic Kidney Disease	16.8%	16.8%
Anemia	19.8%	19.1%
ACS presentation	64.0%	65.7%
Previous PCI	42.3%	42.0%
Previous CABG	10.2%	9.8%
Previous major bleed	0.9%	0.9%

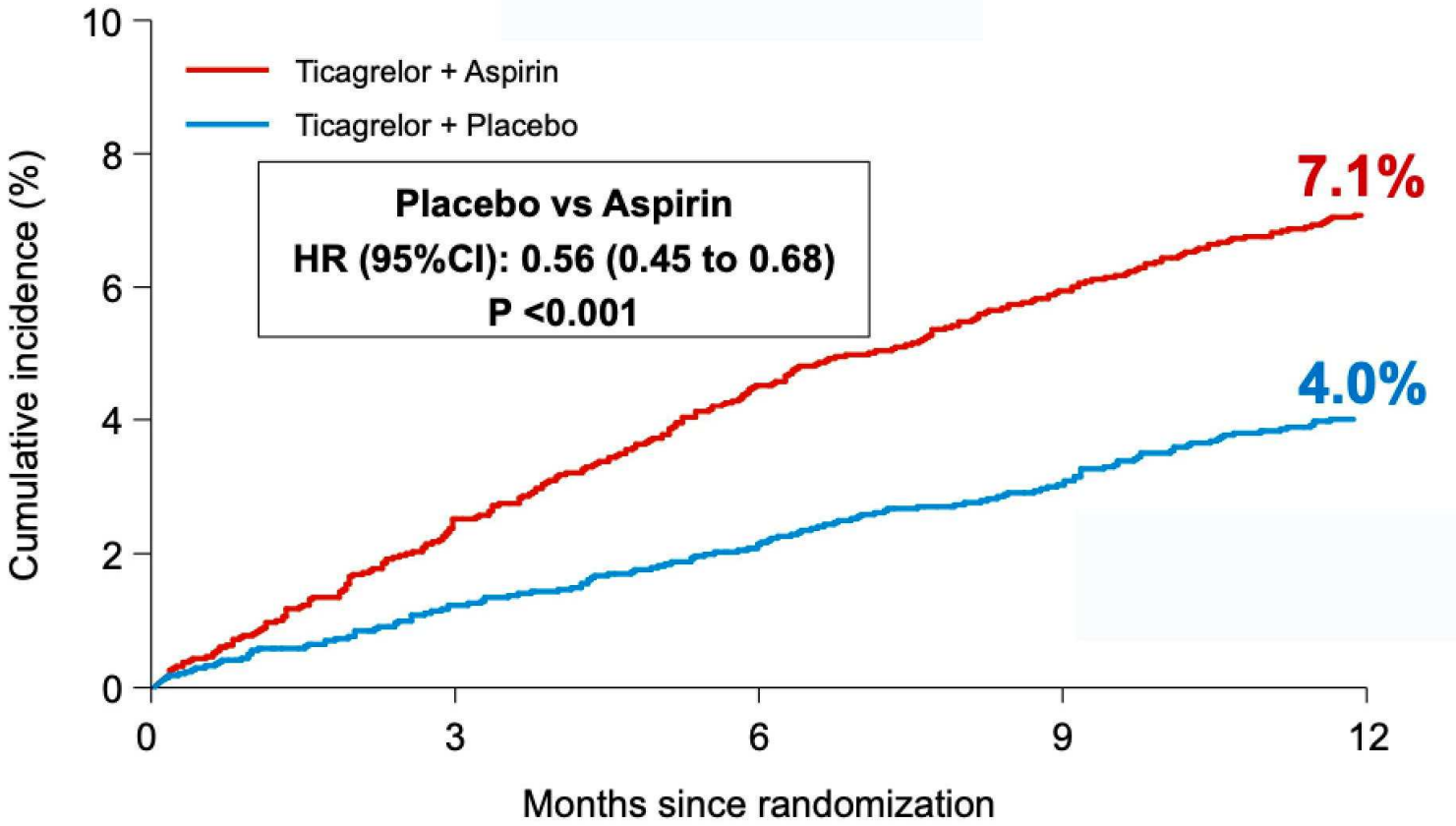
NEJM 2019;381:2032

TWILIGHT : Caractérisrtiques angiographiques

Variable	Tica + Placebo (N = 3555)	Tica + Aspirin (N = 3564)
Radial access	73.1%	72.6%
Multivessel CAD	63.9%	61.6%
Lesion morphology		
Thrombus	10.4%	10.7%
Calcification, moderate/severe	14.0%	13.7%
Any bifurcation	12.2%	12.1%
Total stent length	40.1 ± 24.2	39.7 ± 24.3
Any bifurcation	12.2%	12.1%
Chronic total occlusion	6.2%	6.3%
Total stent length	40.1 ± 24.2	39.7 ± 24.3

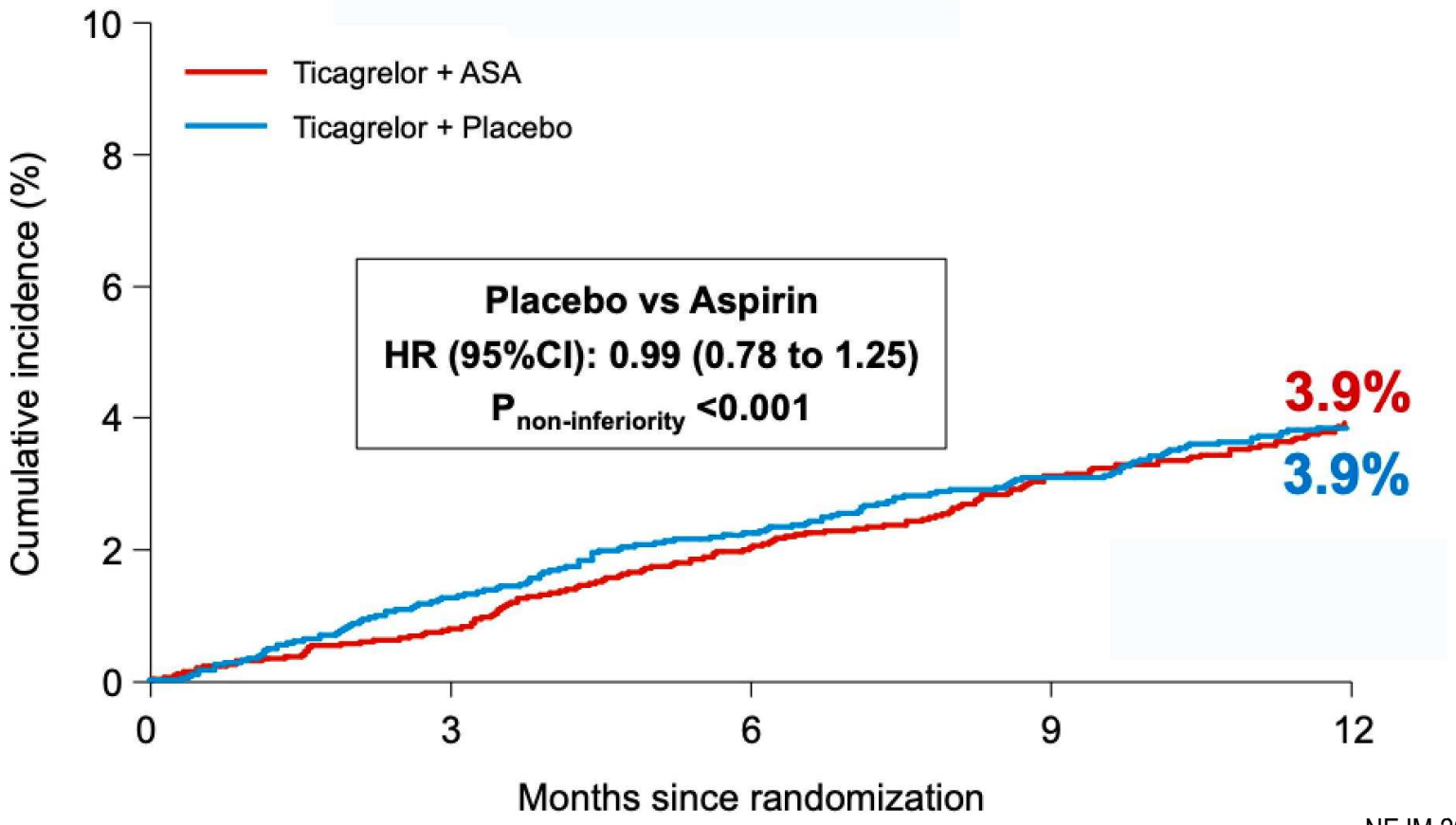
NEJM 2019;381:2032

TWILIGHT : Critère I^{aire} : Saignement BARC≥ 2



NEJM 2019;381:2032

TWILIGHT : Critère II^{aire} : Décès + IDM + AVC



NEJM 2019;381:2032

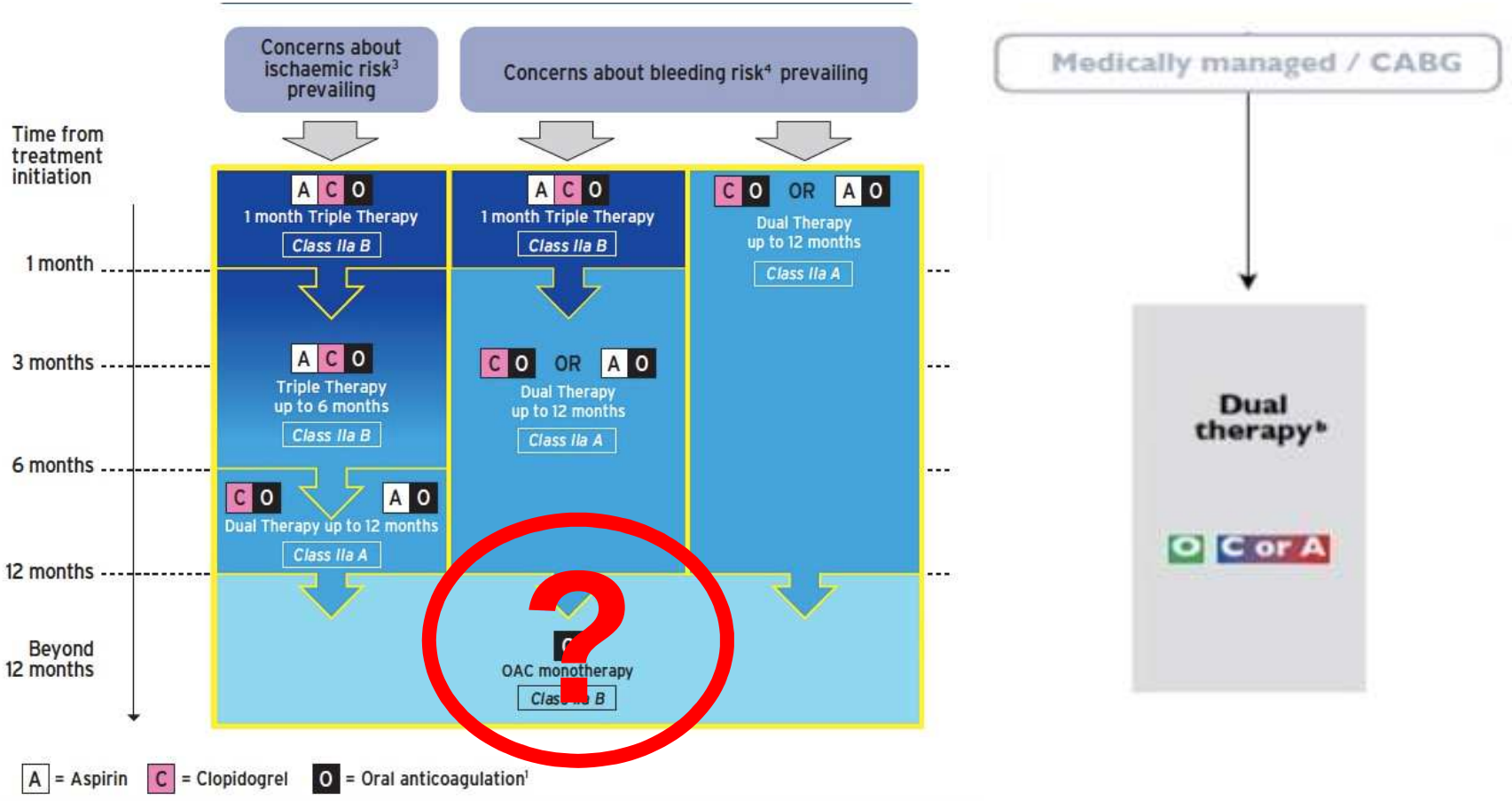
TWILIGHT : Conclusion

In *high-risk* patients who underwent PCI and were treated with ticagrelor and aspirin for 3 months without any major adverse (bleeding or ischemic) events, an antiplatelet strategy of continuing ticagrelor monotherapy resulted in:

- **substantially *less bleeding* than ticagrelor plus aspirin**
- **without increasing ischemic events over a period of *1 year***
  - A lower-than expected incidence of the composite end point of death, MI, or stroke may have biased our results for this key secondary end point toward the null.
  - Lack of power to detect differences in the risk of important yet rare clinical events, such as stent thrombosis and stroke.

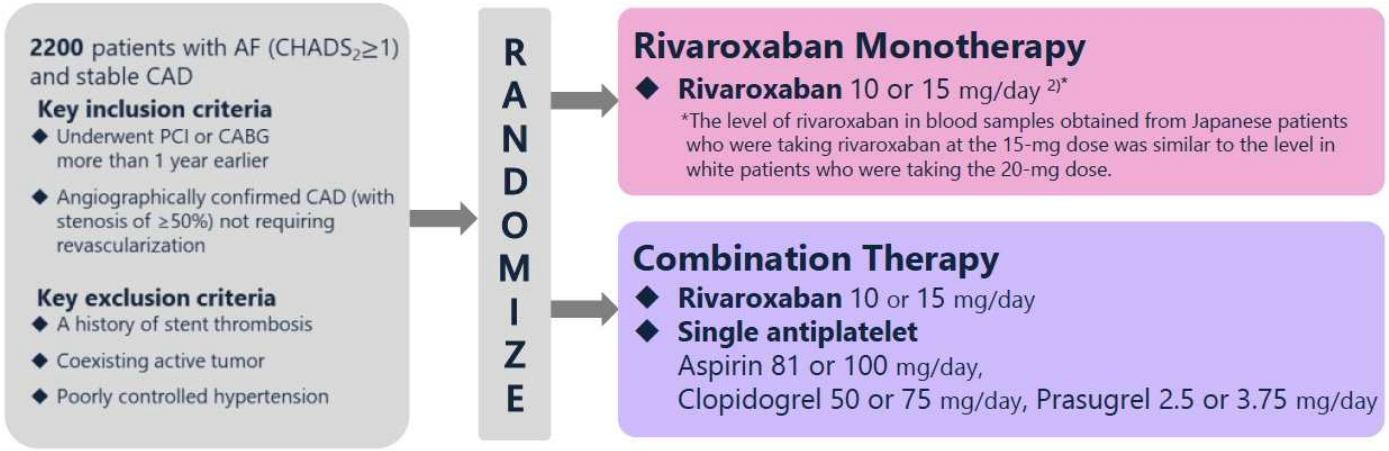
NEJM 2019;381:2032

CORONAROPATHIE & FA
Recommandations ESC 2018



AFIRE

A multicenter, prospective, randomized, open-label, parallel-group trial [1)]

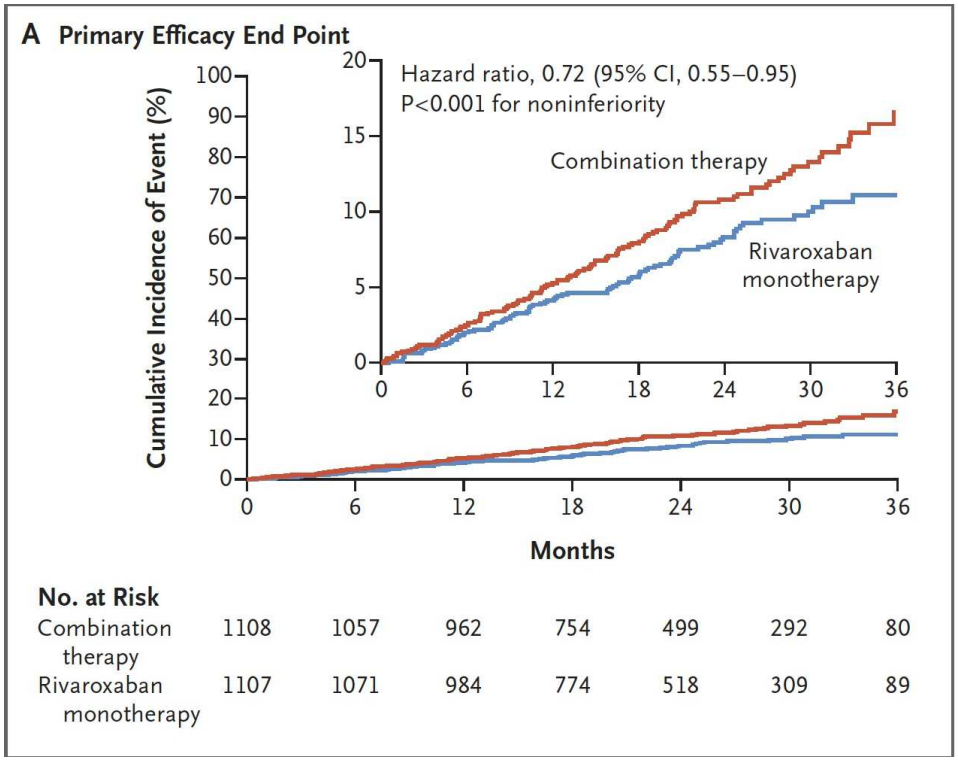


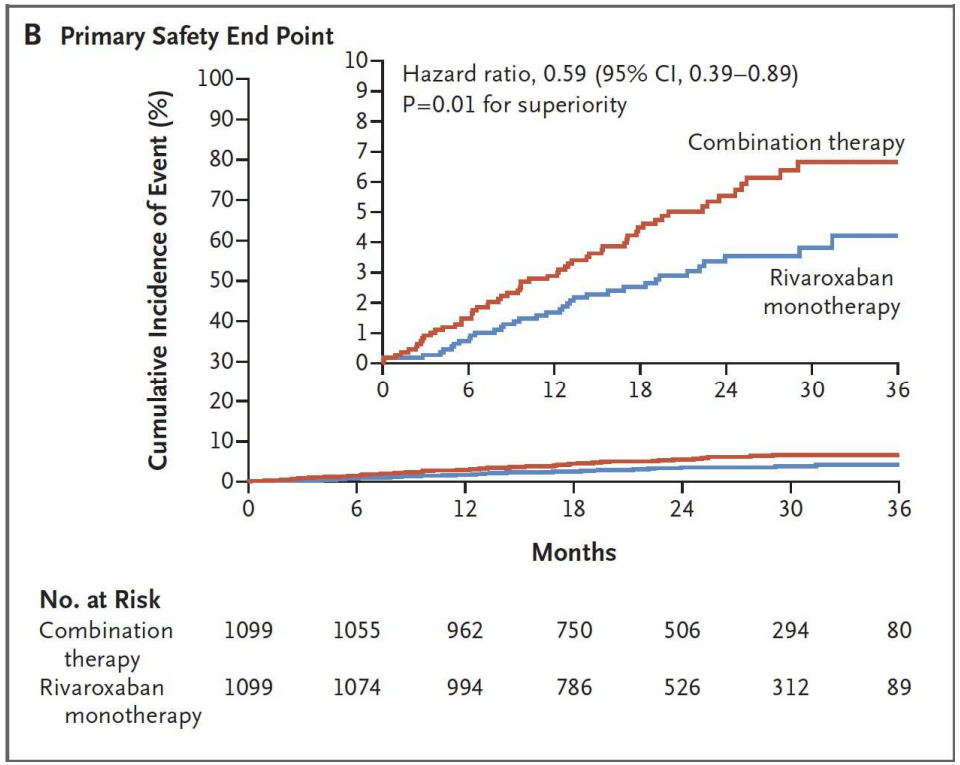
Objectifs :

Non infériorité / efficacité → DC + AVC + embol systémique + IDM + rev urgente pour angor

Supériorité / sécurité → Saignements majeurs

AFIRE : Résultats

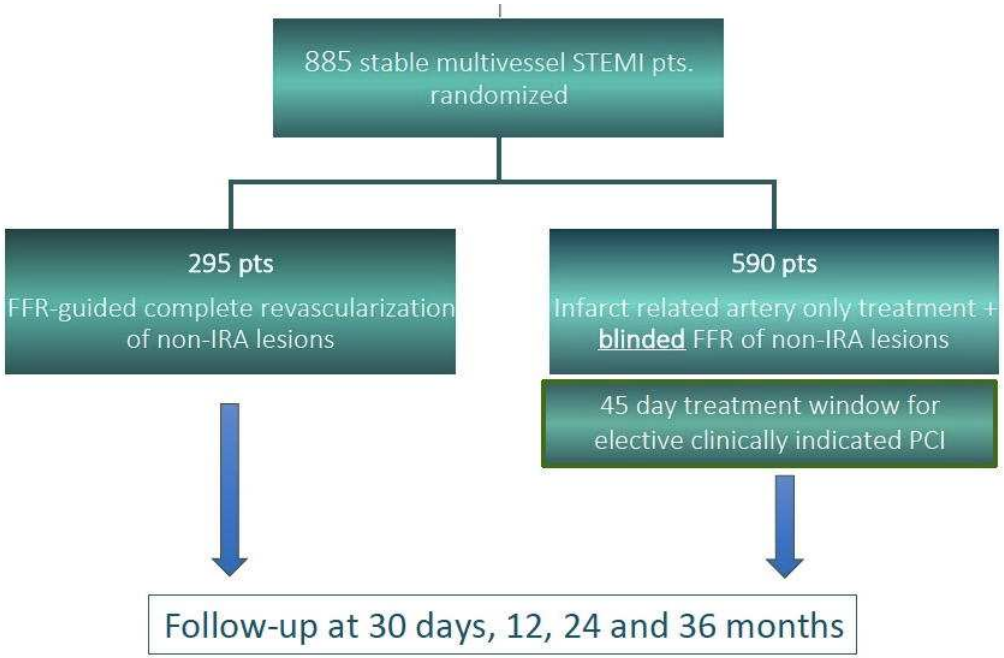




Compare-Acute à 3 ans

FFR guided acute complete revascularization *versus* culprit lesion only treatment in patients presenting with STEMI and multivessel disease;

final 3-year outcome data from Compare-Acute trial



Compare-Acute à 3 ans

Primary endpoint outcome at 3 year

	FFR guided Complete Revascularization (n=295)	Infarct Artery Only treatment (n=590)	HR	95% CI	P value
Primary endpoint	Number of events (%)				
MACCE* (any first event)	46 (15.6%)	178 (30.2%)	0.46	0.33 – 0.64	**<0.001**
Death, all cause	9 (3.1%)	21 (3.6%)	0.86	0.39 – 1.80	0.71
Cardiac	5 (1.7%)	8 (1.4%)	1.25	0.41 – 3.83	0.70
Myocardial infarction (MI)	20 (6.8%)	53 (9.0%)	0.74	0.44 - 1.24	0.28
Spontaneous	17 (5.8%)	40 (6.8%)	0.84	0.48 – 1.49	0.56
Peri-procedural	3 (1.0%)	13 (2.2%)	0.46	0.13 – 1.61	0.19
Revascularization	37 (12,5%)	149 (25.3%)	0.45	0.31 – 0.64	**<0.001**
Urgent	22 (7.5%)	85 (14.4%)	0.46	0.29 – 0.73	**<0.001**
Elective	15 (5.1%)	64 (10.8%)	0.43	0.25 – 0.76	**0.002**
Cerebrovascular event	1 (0.3%)	7 (1.2%)	0.29	0.03 – 2.30	0.24

Popular-Age Trial : Optimal P2Y12 inhibitors > 70 years

	Clopidogrel (n=501)	Ticagrelor/prasugrel (n=502)
Age (years), median (IQR)	77 (73-81)	77 (73-82)
Male	62.7	64.7
BMI (kg/m^2), mean (SD)	26.5 ± 4.4	26.7 ± 4.8
Myocardial infarction	24.4	27.1
PCI	19.6	24.3
CABG	17.0	17.1
Ischemic stroke	4.4	5.0
Diabetes mellitus	29.1	29.9
eGFR <60 (ml/min/1.73m^2)	36.1	37.3
CAG	87.8	90.0
Radial access	73.7	77.1
PCI	47.5	48.9
CABG	15.8	17.4

Popular-Age Trial : Optimal P2Y12 inhibitors > 70 years

	Clopidogrel (n=501)	Ticagrelor/prasugrel (n=502)
Aspirin	85.8	85.6
(N)OAC	16.6	20.3
Ticagrelor		93.8
Prasugrel		2.0
PPI	90.3	90.3
Diagnosis at discharge		
NSTEMI	84.6	83.9
UA	10.8	10.4
Other	4.4	5.7

AFIRE

Primary efficacy end point

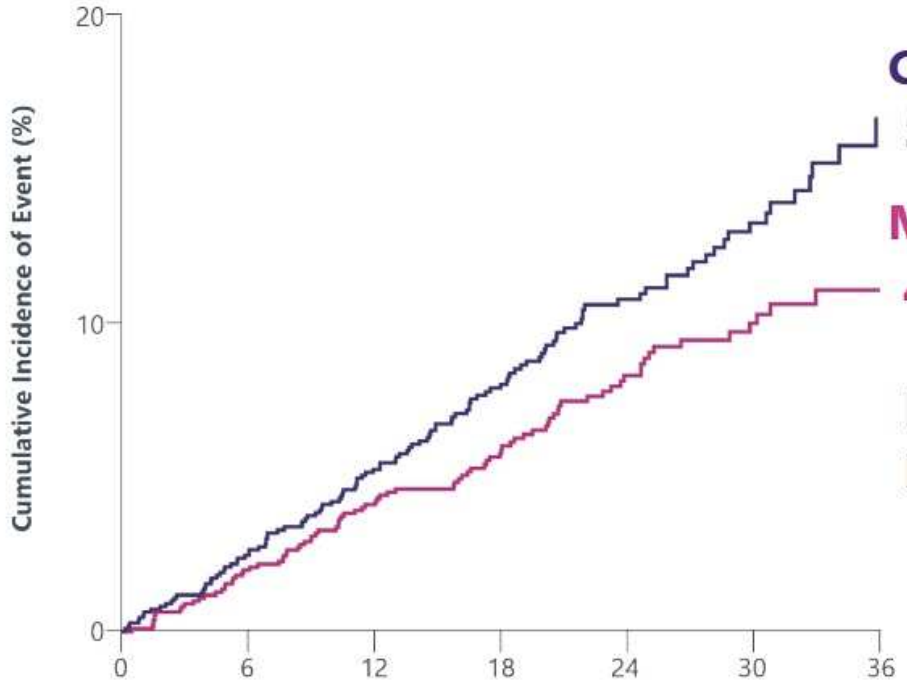
- **The composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause**
- Assessed **noninferiority** of rivaroxaban monotherapy, as compared with combination therapy (**noninferiority margin: 1.46** for the 95% CI, with **a power of 80%)**

Primary safety end point

- To determine superiority of rivaroxaban monotherapy, as compared with combination therapy
- **Major bleeding, as defined according to the criteria of the ISTH***

Kaplan-Meier Estimates of First Occurrence of Primary Efficacy Events

AFIRE



Combination therapy
5.75% per patient-year

Monotherapy
4.14% per patient-year

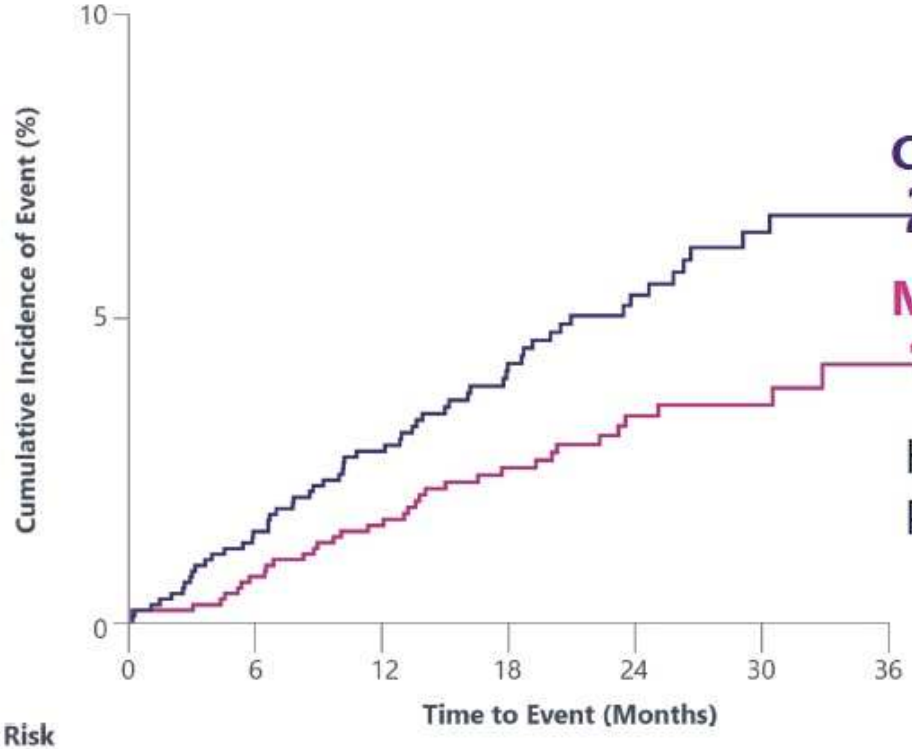
HR, **0.72** (**0.55** to **0.95**)
P<0.001 (noninf.)

*In the assessment for **superiority for the primary efficacy end point** (that was not prespecified), the **P value was 0.02.**

No. at Risk							
Rivaroxaban monotherapy	1107	1071	984	774	518	309	89
Combination therapy	1108	1057	962	754	499	292	80

Kaplan-Meier Estimates of First Occurrence of Primary Safety Events

AFIRE



Combination therapy
2.76% per patient-year

Monotherapy
1.62% per patient-year

HR, **0.59** (**0.39** to **0.89**)
P=0.01 (sup.)

No. at Risk							
Rivaroxaban monotherapy	1099	1074	994	786	526	312	89
Combination therapy	1099	1055	962	750	506	294	80

The Respective Incidence Rates of Secondary End Points

AFIRE

End Point – no. (% per patient-year)	**Rivaroxaban Monotherapy**	**Combination Therapy**	**HR (95% CI)***
All-cause death #	41 (1.85)	73 (3.37)	0.55 (0.38 to 0.81)
Cardiovascular	26 (1.17)	43 (1.99)	0.59 (0.36 to 0.96)
Noncardiovascular	15 (0.68)	30 (1.39)	0.49 (0.27 to 0.92)
CV events			
Ischemic stroke #	21 (0.96)	28 (1.31)	0.73 (0.42 to 1.29)
Hemorrhagic stroke #	4 (0.18)	13 (0.60)	0.30 (0.10 to 0.92)
Myocardial infarction #	13 (0.59)	8 (0.37)	1.60 (0.67 to 3.87)
Unstable angina requiring revascularization	13 (0.59)	18 (0.84)	0.71 (0.35 to 1.44)
Systemic embolism	2 (0.09)	1 (0.05)	1.97 (0.18 to 21.73)
Bleeding events			
Major bleeding #	35 (1.62)	58 (2.76)	0.59 (0.39 to 0.89)
Nonmajor bleeding	121 (5.89)	198 (10.31)	0.58 (0.46 to 0.72)
All bleeding	146 (7.22)	238 (12.72)	0.58 (0.47 to 0.71)
Net adverse clinical events	84 (3.90)	131 (6.28)	0.62 (0.47 to 0.82)

* The 95% CIs presented in this table have not been adjusted for multiplicity; therefore, # Components of net adverse clinical events.

AFIRE CONCLUSION

The AFIRE study demonstrated that **rivaroxaban monotherapy** was **noninferior** to **combination therapy** with rivaroxaban plus an antiplatelet agent with respect to **CV events and death from any cause** and **superior** with respect to **major bleeding** in patients with AF and stable CAD.